



*This edition is produced in compliance with the Government's regulations for conserving paper and other essential materials*

## CONTENTS

### SYMPOSIUM ON NEUROPSYCHIATRIC DISEASES

	PAGE
Acute Encephalo myelo radiculoneuritis (Guillain Barré Syndrome) By Dr Roland P Mackay	1
The Diagnosis and Surgical Treatment of Peripheral Nerve Injuries By Dr Ioyal Davis	9
The Organic Origin of Apparent Functional Nervous Disease By Dr LeRoy H Sloan	30
Benign Lymphocytic Choriomeningitis By Dr Loren William Avery	36
Pathologic Pyramidal Tract Signs By Dr Victor E. Gonda	45
Subdural Hematoma By Dr Eric Oldberg	62
The Relief of Facial Pain By Dr A Earl Walker	73
Chordotomy for Intractable Pain By Dr Adrien H Verbruggen	98
Protrusion of the Intervertebral Disk By Dr Harold C. Voris	111
Management of Myasthenia Gravis By Dr Richard Richter	126
Periarteritis Nodosa By Drs George W Scupham and Janet R Kinney	139
The Modern Concept of Schizophrenia By Drs L J Meduna and W S McCulloch	147



## CONTENTS

The Feasibility and Advantages of Outpatient Electroshock Therapy for the Mentally Ill	165
By Drs John J Madden and Joseph A. Luhan	
Insomnia	178
By Dr Meyer Solomon	
Insanity and the Criminal	195
By Drs William H. Humes and Harry R. Hoffman	
CLINICS ON OTHER SUBJECTS	
Uses and Abuses of Quinidine	215
By Dr J. Bailey Carter	
Pernicious Anemia	229
By Drs George E. Farrar, Jr. and Harold L. Hyman	
The Rational Endocrine Therapy of Menstrual Disorders	251
By Dr A. F. Rakoff	
Cumulative Index	269

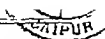
# THE MEDICAL CLINICS of

## NORTH AMERICA

Vol-29

1945

CHICAGO NUMBER



### SYMPOSIUM ON NEUROPSYCHIATRIC DISEASES

#### ACUTE ENCEPHALO MYELO RADICULONEURITIS (GUILLAIN BARRÉ SYNDROME)

ROLAND P. MACKAY, M.D.\*

WE have for presentation and discussion today three cases representing a neurologic condition apparently quite common, and yet frequently not recognized. Many more cases could be presented, but these three suffice to illustrate variant forms of the disorder.

**CASE I**—O. D., a white, unmarried man aged 40, was admitted to the Illinois Neuropsychiatric Institute on March 30, 1944, complaining of "sinus trouble" and deviation upward of the left eye for six weeks and weakness of all the extremities of the body for two weeks. About February 20 he had had a "cold" with nasal obstruction and some swelling of the left cheek. A week later the left eye had turned upward and paralysis of the left side of the face was noted. About two weeks later numbness of the left side of the face had appeared, with weakness of the right arm.

He was then (March 20) admitted to the service of Dr. Paul Bucy at the Chicago Memorial Hospital where examination revealed marked weakness of the left inferior rectus muscle, the left side of the face and weakness of abduction of the right arm together with slight impairment of sensibility to pain and touch over the left side of the face. His temperature was normal and his blood pressure 168/112. The spinal fluid was clear and colorless and under a pressure of 130 mm. of water. The cell count was zero and total protein content 80.

From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine, and the Illinois Neuropsychiatric Institute, Chicago.  
Professor of Neurology, University of Illinois College of Medicine.

mg per 100 cc Gold curve was 0033310000 X-rays revealed clouding of the left frontal, ethmoid and maxillary sinuses, and apical infection of a lower molar tooth A day after discharge from the Chicago Memorial Hospital the patient noted weakness of both lower extremities and tingling paresthesias in all four extremities

On March 30, *examination* at the Illinois Neuropsychiatric Institute revealed weakness of outward and downward gaze of the left eye The left pupil was larger than the right, and both were sluggish to light and in accommodation There was weakness of the left side of the face and deviation of the uvula toward the right on phonation There was also muscular weakness of all four extremities, chiefly proximal All deep tendon reflexes were absent, and the abdominal reflexes were doubtfully present The Babinski responses were normal Superficial sensation was all normal except for slight hyperesthesia below the left eye Vibratory sensation was diminished and proprioceptive sensation lost in the lower extremities The muscles of the extremities were tender Within the next few days his condition deteriorated, with weakness spreading to involve the left sternomastoid and trapezius muscles The sphincters functioned normally

*Laboratory examination* of the urine and blood gave only normal findings The spinal fluid was examined five times The results are shown in the following table On all occasions the fluid was clear and colorless, with normal pressure and response to jugular compression

Date	Cells	Pandy Test	Total Protein, Mg per 100 Cc	Sugar, Mg per 100 Cc	Chlondes, Mg per 100 Cc	Wassermann Test	Gold Reaction
3/20	0	—	80				0033310000
4/1	1	2 plus	111			Negative	0001233210
4/9	2	2 "	150				
4/28	6	3 "	221		771		
5/23	2	2 "	220	63			0000023432
6/29	3	1 "	170				

This patient remained in the hospital for three months During the first portion of his stay his neurological abnormalities increased Vibratory and proprioceptive sensibility decreased in the upper extremities, and his dysphonia and dysphagia continued Respirations were seriously embarrassed He was treated with large amounts of vitamins B and C and crude liver extract Physiotherapy was also administered in the form of heat, massage and exercises Suddenly, on June 12 he improved abruptly and thereafter gained ground rapidly He was able to walk on June 18, and on June 30 he was discharged with instructions to continue to take vitamins orally His diplopia, due to persisting weakness of the left oculomotor nerve, was still present, though diminished when he left

In this case a healthy man, after an upper respiratory infection developed an extensive polyneuritis with involvement of cranial as well as spinal nerves and markedly elevated total protein content of the spinal fluid without increase of the cell count. Though delayed recovery came in four months after the onset, and was practically complete. Note that in this case the elevated protein content of the cerebrospinal fluid gave indication of inflammatory change in the spinal and cranial nerve roots, but there was no clear evidence of pathologic change within the brain or spinal cord. The level of total protein in the cerebrospinal fluid rose during the first part of his stay in the hospital, and later declined, but was still quite high when he left the hospital almost well.

In the following case a very similar series of events is seen.

**CASE II**—O. W., a colored married man, aged 44, was admitted to the Illinois Neuropsychiatric Institute on May 14, 1944, complaining of progressive weakness of his extremities for twelve days and difficulty in swallowing, and hoarseness for three days. Four weeks previously he had contracted a cold with aching pains in his back and legs. Twelve days before admission he had noted weakness and sharp pains in his extremities.

The diagnosis of polyneuritis had been made by Dr. Paul Bucy upon the patient's admission to the Chicago Memorial Hospital on May 5, 1944. There the cerebrospinal fluid contained 42 mg. of total protein per 100 cc., with 3 cells per cubic millimeter (see accompanying table). The weakness in his lower extremities increased with additional paresthesias after his return home. Dysphonia and dysphagia began three days before admission.

General *examination* revealed a temperature of 101° F., a pulse rate of 128, and respirations of 28. He was coughing up much sputum and presented signs of pneumonia in the right upper lobe. Neurologically he was hoarse and unable to swallow. There was marked weakness in the upper extremities and complete paralysis of the lower, worse proximally. Beevor's sign was present. All deep reflexes were absent, the abdominal reflexes were diminished and there was no response to plantar stimulation. Vibratory sensibility was absent in both lower extremities and diminished in the right upper. Superficial sensibility was reduced over the feet, calves and posterior portions of the thighs. The muscles of the extremities were tender.

*Laboratory studies* were normal except for a leukocyte count of 24,250, a figure which steadily declined to 10,100 within two weeks. Additional spinal punctures gave the findings shown in the table. One should note the increased content of total protein with normal cell count. On all occasions the fluid was clear and colorless with normal pressure and dynamics.

mg per 100 cc Gold curve was 0033310000 X-rays revealed clouding of the left frontal, ethmoid and maxillary sinuses, and apical infection of a lower molar tooth A day after discharge from the Chicago Memorial Hospital the patient noted weakness of both lower extremities and tingling paresthesias in all four extremities

On March 30, *examination* at the Illinois Neuropsychiatric Institute revealed weakness of outward and downward gaze of the left eye The left pupil was larger than the right, and both were sluggish to light and in accommodation There was weakness of the left side of the face and deviation of the uvula toward the right on phonation There was also muscular weakness of all four extremities, chiefly proximal All deep tendon reflexes were absent, and the abdominal reflexes were doubtfully present The Babinski responses were normal Superficial sensation was all normal except for slight hyperesthesia below the left eye Vibratory sensation was diminished and proprioceptive sensation lost in the lower extremities The muscles of the extremities were tender Within the next few days his condition deteriorated, with weakness spreading to involve the left sternomastoid and trapezius muscles The sphincters functioned normally

*Laboratory examination* of the urine and blood gave only normal findings The spinal fluid was examined five times The results are shown in the following table On all occasions the fluid was clear and colorless, with normal pressure and response to jugular compression

Date	Cells	Pandy Test	Total Protein, Mg per 100 Cc	Sugar, Mg per 100 Cc	Chlorides, Mg per 100 Cc	Wassermann Test	Gold Reaction
3/20	0	—	80				0033310000
4/1	1	2 plus	111			Negative	0001233210
4/9	2	2 "	150				
4/28	6	3 "	221		771		
5/23	2	2 "	220	63			0000023432
6/29	3	1 "	170				

This patient remained in the hospital for three months During the first portion of his stay his neurological abnormalities increased Vibratory and proprioceptive sensibility decreased in the upper extremities, and his dysphonia and dysphagia continued Respirations were seriously embarrassed He was treated with large amounts of vitamins B and C and crude liver extract Physiotherapy was also administered in the form of heat, massage and exercises Suddenly, on June 12 he improved abruptly and thereafter gained ground rapidly He was able to walk on June 18, and on June 30 he was discharged with instructions to continue to take vitamins orally His diplopia, due to persistent weakness of the left oculomotor nerve, was still present, though improved, when he left

In this case a healthy man, after an upper respiratory infection, developed an extensive polyneuritis with involvement of cranial as well as spinal nerves and markedly elevated total protein content of the spinal fluid without increase of the cell count. Though delayed recovery came in four months after the onset, and was practically complete. Note that in this case the elevated protein content of the cerebrospinal fluid gave indication of inflammatory change in the spinal and cranial nerve roots, but there was no clear evidence of pathologic change within the brain or spinal cord. The level of total protein in the cerebrospinal fluid rose during the first part of his stay in the hospital, and later declined, but was still quite high when he left the hospital almost well.

In the following case a very similar series of events is seen.

CASE II—O. W., a colored married man, aged 44, was admitted to the Illinois Neuropsychiatric Institute on May 14, 1944, complaining of progressive weakness of his extremities for twelve days and difficulty in swallowing, and hoarseness for three days. Four weeks previously he had contracted a cold with aching pains in his back and legs. Twelve days before admission he had noted weakness and sharp pains in his extremities.

The diagnosis of polyneuritis had been made by Dr. Paul Bucy upon the patient's admission to the Chicago Memorial Hospital on May 5, 1944. There the cerebrospinal fluid contained 42 mg. of total protein per 100 cc. with 3 cells per cubic millimeter (see accompanying table). The weakness in his lower extremities increased with additional paresthesias after his return home. Dysphonia and dysphagia began three days before admission.

General examination revealed a temperature of 101° F., a pulse rate of 128, and respirations of 28. He was coughing up much sputum and presented signs of pneumonia in the right upper lobe. Neurologically he was hoarse and unable to swallow. There was marked weakness in the upper extremities and complete paralysis of the lower, worse proximally. Beevor's sign was present. All deep reflexes were absent, the abdominal reflexes were diminished and there was no response to plantar stimulation. Vibratory sensibility was absent in both lower extremities and diminished in the right upper. Superficial sensibility was reduced over the feet, calves and posterior portions of the thighs. The muscles of the extremities were tender.

Laboratory studies were normal except for a leukocyte count of 24,250, a figure which steadily declined to 10,100 within two weeks. Additional spinal punctures gave the findings shown in the table. One should note the increased content of total protein with normal cell count. On all occasions the fluid was clear and colorless with normal pressure and dynamics.

Date	Cells	Pandy Test	Total Protein, Mg per 100 Cc	Wassermann Test	Gold Reaction
5/5	3	trace	42	Negative	0000000000
5/14	0	1 plus	200	"	0001233332
6/5	3	1 "			0000122110
6/16	4	1 "	180		

Blood culture on admission gave hemolytic *Staphylococcus aureus*, and culture of the sputum showed a pure growth of *Pseudomonas albuginosa*

*Course* The patient was given sulfadiazine by mouth and a diet high in calories and vitamins. Crude liver extract and high doses of ascorbic acid, thiamine hydrochloride and niacinamide were given every day intramuscularly. The pneumonia gradually cleared but respiratory paralysis increased markedly so that the use of a respirator was seriously considered. On May 22 both respiration and swallowing improved rapidly and motor strength increased, first in the upper and then in the lower extremities. By July 22 the patient was able to walk with some weakness, and was discharged.

Again, we note the occurrence of an upper respiratory infection followed in about two weeks by the onset of paralytic disorders. Here, the weakness appeared first in the lower extremities, in the first case certain of the cranial nerves were primarily affected. The onset of the paralysis in the second case was soon followed by bronchopneumonia which was mild and rapidly responded to treatment with sulfadiazine. The extreme degree of paralysis of the lower motor neuron may have masked reflex evidences of implication of the central nervous system, but at any rate no such evidences were found.

In the third and final case to be presented a much more severe and persistent neurologic disturbance may be seen. The clinical involvements were far more extensive, and differed somewhat from those observed in the first two cases, but sufficient similarity existed for us to recognize the same general type of disease.

**CASE III**—G L, a white, married woman, aged 40, with two children, was admitted to St Luke's Hospital in Chicago on April 1, 1944, complaining of marked weakness of the left arm, "numbness" of both arms and the left leg, and pains in the neck and shoulder for three weeks.

Early in January she had had anorexia, and on January 20 had felt ill, had a slight fever, and vomited. For two weeks thereafter she had hiccoughs intermittently. Early in March she began to have pain

in the left shoulder and arm, and soon this pain extended to involve, in order, the left lower, the right lower, and the right upper extremities. There was a sense of compression in the left side of the thorax and abdomen. The pain was a dull ache with occasional sharp stabs, subsiding to leave an itching sensation. Within a few days numbness began in all extremities, particularly on the left.

About March 22 weakness appeared in the left upper and lower extremities and grew worse. She could no longer tell where the left forearm was. Pains, drawing sensations and feelings of tightness continued.

*Examination* on admission revealed an emaciated woman, with normal cranial nerves. The left upper extremity was moderately weak and atrophy had produced a *main en griffe* deformity in the left hand. Occasional atetoid movements were seen in this hand. There was slight weakness in the left lower extremity. The tendon reflexes were markedly reduced in both left extremities and the right ankle jerk was barely elicitable. Abdominal reflexes were absent on the left and sluggish on the right. The Babinski reflex was positive on the left and equivocal on the right. Sensibility to pain, touch, heat and cold was reduced in the left upper extremity and over the upper half of the thorax on the left. Both vibratory and position sensibility was markedly reduced in the whole left upper extremity, with complete stereoaesthesia. Vibratory sensibility was moderately reduced in both ankles. There was definite tenderness in the calves and shoulders and in the left arm.

*Laboratory studies* The Kahn test of the blood was negative. Erythrocytes numbered 372 million, leukocytes 5100, and hemoglobin content was 11.3 gm per 100 cc. Gastric analysis revealed 20 units of free acid, 5 of combined acid.

Cerebrospinal fluid was clear and colorless and under pressure of 96 mm of water, with normal dynamics. The total protein content was elevated to 50 mg per 100 cc. The cell count was 25 (see table). Three days later a second spinal picture showed no cells and total protein of 30 mg per 100 cc. Roentgenograms revealed slight osteoarthritis of the cervical spine.

Date	Cells	Pandy Test	Total Protein Mg per 100 Cc	Wassermann Test	Gold Reaction
4/4	25	2 plus	50	Negative	0001100000
4/7	0	1	30		1123331000
5/11	10	1	45		1122321000
5/24	0		50		0012231100

The patient remained practically afebrile. Some weakness began to appear also in the right arm. Three intravenous injections of typhoid



vaccine gave temperatures of 102.6°, 101.8°, and 100.6° F respectively, and no clinical change. She was treated with niacinamide and thiamine hydrochloride in doses of 100 mg each, daily. Because of the expense of hospitalization, she was discharged on April 17.

*Interval history* At home the patient had severe night sweats, the right arm became weaker, the left a little stronger. She experienced frontal headaches and muscular cramps in both legs.

*Rehospitalization* The patient was rehospitalized on May 9 in the Illinois Neuropsychiatric Institute. Neurologic examination revealed essentially unchanged findings except for slight inequality of the pupils, weakness of the sternomastoid muscles, and definitely more marked paresis of the right arm and leg. During her stay in this hospital there was slow improvement in the power of the left upper extremity. The legs became slightly spastic with increased knee and ankle jerks. The cerebrospinal fluid was examined on two occasions, and showed slightly elevated protein content without increased cell count (see table). Cramps continued in the lower extremities despite administration of calcium and phenobarbital. Multiple vitamin preparations were given parenterally in large doses, as well as crude liver extract. Physiotherapy included heat, massage and muscle reeducation. The patient was allowed to return home on July 22 still unable to walk, still not greatly improved above her condition on admission.

In this unusual case we note an onset with vague symptoms suggesting encephalitis, with vomiting and hiccoughs, followed by pains, paresthesias and weakness in first the left upper, then the left lower, then the right lower, and finally the right upper extremity. There were indubitable evidences of involvement of the central nervous system, such as the marked loss of proprioceptive and vibratory sensibility in the left arm, the mild athetosis in the left hand, the gradually increasing spasticity in the lower extremities and the pathologic Babinski responses. Yet the paresthesias, pains and tenderness, as well as the atrophy indicated disturbances in the nerves and roots. The cranial nerves escaped all but minor damage. The cerebrospinal fluid vaguely suggested elevation of total protein without increase of cells, but not strongly. Finally, the patient failed to make more than slight improvement during over four months of illness, despite intensive hospital management.

#### COMMENT

In the first two cases one must diagnose the condition as acute infectious radiculoneuritis with albuminocytologic dissociation. In the third the diagnosis must be acute infectious encephalo-myelo-radiculoneuritis with a tendency to albuminocytologic dissociation. Reference to other cases which might have been reported, and to numerous

cases in medical literature, indicates that our three patients suffered from a condition of considerable variability and pleomorphism, and yet characterized by some combination of signs and symptoms of which our third patient presented almost the complete catalog

**Historical**—Although previous reports had been made, Osler, in 1892, first definitively described "acute infectious polyneuritis" Mills, in 1898, used the term "neuritis" for the first time. In 1916 Patrick noted the frequent occurrence of facial paralysis in association with acute polyneuritis. In the same year 1916, Guillain, Barré and Strohl first drew attention to the tendency in the cerebrospinal fluid toward elevation of the total protein with little or no increase in the cell content, the so-called albuminocytologic dissociation. Shortly thereafter a number of other reports appeared, including one by Bradford, Bashford and Wilson in 1918, in which evidence was presented for the virus etiology of this disease though their results could never be confirmed. Recent worthy reviews are those of De Jong in 1940 and Roseman and Aring in 1941.

**Definition**—Acute infectious encephalo-myeo-radicleoneuritis is an acute, pleomorphic disease of the nervous system, usually following an upper respiratory infection, and characterized by paresthesias and pains, widespread neuritic motor weakness of the extremities and frequently involving the seventh or other cranial nerves and sometimes the cerebrospinal axis and often associated with elevation of the total protein content of the cerebrospinal fluid without significant increase of the cell content. The unwieldy name results from the potential involvement of the brain, spinal cord, nerve roots and peripheral nerves. In many cases one or more of these features may be absent, the brain and spinal cord frequently escaping injury as judged by the clinical features. In a varying percentage of cases (14 to 42 per cent) death follows in the acute stage but in the majority complete recovery is achieved after several weeks or months, although persistent neurologic damage has been recorded in some cases, as in our Case III.

**Clinical Features**—Any age group may be attacked. The outstanding neurologic features are the paresthesias and pains, the motor weakness of the lower neuron type, and the diminution or loss of the tendon reflexes. Tenderness of the affected muscles may be striking. Paralysis of the face on one or both sides is not uncommon, and other cranial nerves are only less frequently involved. Invasion of the spinal cord or brain may be indicated by the presence of pathologic reflexes, mental abnormalities, hyperkinesias or papilledema. The presence of albuminocytologic dissociation is observed in more than half of the cases. Sphincters are usually spared. Although the onset and invasion

of the disease are usually acute, recovery may be prolonged. Etiology is unknown, but the disease is generally supposed to be due to a virus.

**Pathologic Features**—The chief pathologic abnormalities are degeneration of the roots and peripheral nerves, sometimes with cellular infiltrations, and congestion of the nerves and often of the spinal cord. Cellular degenerations reported in the neuraxis have regularly been mild or doubtful, but those in the dorsal root ganglia indisputable.

**Diagnosis**—Diagnosis is not difficult if one requires the presence of more than one or two of the clinical features. Poliomyelitis may cause some difficulty, but the presence of sensory changes and the frequent albuminocytologic dissociation should serve to distinguish the disease under discussion. Albuminocytologic dissociation alone is not sufficient for the diagnosis, since it may be absent, or may be found in other forms of polyneuritis, such as postdiphtheritic type. Polyneuritis of other types are to be distinguished by the history, the absence of albuminocytologic dissociation, and the absence of features suggesting involvement of the neuraxis. Landry's ascending paralysis—an unfortunate term signifying cephalad progression—may be caused by the disease under discussion, but it may also be caused by poliomyelitis, thrombosis of the anterior spinal artery and probably other conditions as well.

**Treatment**—Treatment must be only symptomatic until more is known of the cause of the disease. Vitamin B should be given in abundance, with careful nursing directed to the prevention of bed-sores and adequate nutrition. Respiratory paralysis may require the use of a respirator. Physiotherapy may be very useful after the acute stage in the prevention of contractures and the restoration of maximal muscular function.

#### BIBLIOGRAPHY

- 1 Osler, William. *Principles and Practice of Medicine*. New York, D Appleton and Co. 1892.
- 2 Mills, C K. The Reclassification of Some Organic Nervous Diseases on the Basis of the Neurone. *J.A.M.A.*, 31:11-13, 1898.
- 3 Patrick, Hugh T. Facial Diplegia in Multiple Neuritis. *J Nerv & Ment Dis.*, 44:322-333 (Oct.) 1916.
- 4 Guillain, Georges, Barre, J-A and Strohl, A. Sur un syndrome de radiculonevrite avec hyperalbuminose du liquide cephalo-rachidien sans reaction cellulaire. *Bull et Men Soc Med d'hôp de Paris*, 40:462 (Oct 13) 1916.
- 5 Bradford, John Rose, Bashford, E F and Wilson, J A. Acute Infective Polyneuritis. *Quart J Med.*, 12:88 (Oct-Jan) 1918-1919.
- 6 DeJong, Russell N. The Guillain-Barre Syndrome. Polyradiculoneuritis with Albuminocytologic Dissociation. *Arch Neurol & Psychiat.*, 44:1044 (Nov) 1940.
- 7 Roseman, E and Aring, C D. Infectious Polyneuritis, Infectious Neuritis, Acute Polyneuritis with Facial Diplegia, Guillain-Barré Syndrome, Landry's Paralysis, etc. *Medicine*, 20:463, 1941.

## THE DIAGNOSIS AND SURGICAL TREATMENT OF PERIPHERAL NERVE INJURIES

LOYAL DAVIS, PH D, M D, D Sc.\*

DEJERINE, a great French neurologist, once said, "Nerve wounds are still a mysterious disturbing problem to many doctors' Injuries to peripheral nerves in civil life are sufficiently infrequent so that no one individual has been able to gather enough personal cases to make a thoroughly profitable clinical investigation As a result, the greater part of our knowledge concerning these injuries has come from World War I and prior to that, the Civil and Russo-Japanese Wars

Unfortunately however, much of the clinical work that was done upon peripheral nerve injuries in the last war was wasted because of the fact that the records were incomplete and no proper follow-up of the surgical procedures which were done was ever possible. It is to be hoped that at least one of the contributions to humanity from this present world conflict may come from a study of the compilation of records upon the numerous peripheral nerve injuries which have occurred This can only be accomplished, however, by coordination of the Army and Navy medical services and those agencies which deal with the veteran after his discharge, to the end that complete follow-up records of the return of sensation and motion following surgical procedures may be obtained by making the veteran's compensation contingent upon his examination by competent neurologists and neurological surgeons at intervals for a sufficient length of time to draw conclusions from his case

The subject of peripheral nerve injuries is an enormous one and a clinic could be devoted to any one of the many aspects of that subject However, there are a few fundamental facts concerning the diagnosis and treatment of peripheral nerve injuries which should be emphasized and which afford a practical working knowledge sufficient to enable the physician to arrive at a correct diagnosis and advise his patient what can and should be done to regain a useful extremity The most commonly injured nerves are those of the upper extremity the radial the median and the ulnar These are also the nerves when injured, which produce the most disabling function to the patient because they involve the use of his hand It is important

---

\* Professor and Chairman Division of Surgery, Northwestern University Medical School Attending Surgeon Passavant Memorial Hospital, Chicago

to make an early diagnosis to secure apposition of divided nerve ends so that regeneration may occur promptly and function return to the hand or the upper extremity before atrophy of muscles and fibrosis of joints have made the effector mechanism so ineffective that it matters little whether nerve regeneration takes place

### RADIAL NERVE INJURIES

The characteristic deformity of a radial nerve lesion, which occurs most commonly as the radial nerve winds around the humerus in the upper arm, is that of a dropped wrist and fingers (Fig 1) The hand cannot function properly when the wrist is flexed As Kanavel pointed



Fig 1—Drop-wrist deformity of a radial nerve lesion

out many years ago, the position of function of the hand is that of slight dorsiflexion at the wrist, extension of the proximal phalanges at the metacarpophalangeal joints, and semiflexion of the terminal two phalanges with the thumb adducted toward the palm of the hand One can test the power of the hand by attempting to make a fist with the wrist in flexion As a matter of fact, when a fist is made the hand immediately assumes the position of dorsiflexion

When the radial nerve is injured in the arm, paralysis of the extensors of the wrist, fingers and thumb occurs If the lesion occurs high in the arm there is also a paralysis of the triceps muscle and inability to extend the forearm at the elbow The radial nerve is almost purely motor and has a small sensory component, so that there may

be a loss of sensation only in that area bounded by the first metacarpal of the index finger and the metacarpal of the thumb. This is the area of isolated supply to pinprick sensation. The anatomical supply of the radial nerve has a much larger extent but in the presence of intact median and ulnar nerves the overlap of sensation to pinprick may be so great that the insensitive area is only that small area of skin just described (Fig 2)

When testing the ability of the patient with a radial nerve lesion to extend the fingers, the thumb or the wrist, it is necessary that the palm of the hand be placed flat on the table and the patient then be asked to extend his wrist or fingers. If this position is not assumed it is possible for the patient to flex his fingers strongly, and for the wrist to assume passively a position of dorsiflexion which may be mistaken for a pure extensor movement. Likewise, when testing for

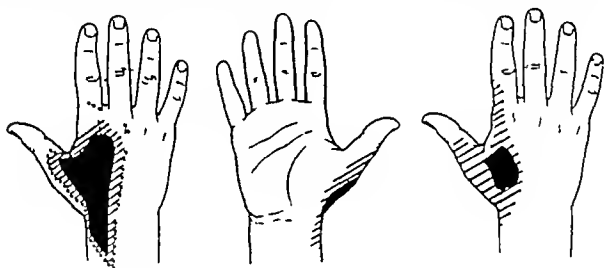


Fig 2—Types of loss of sensation in a radial nerve lesion

extension of the fingers they must be placed flat on the table and then the patient must be asked to extend them

#### MEDIAN NERVE INJURIES

Certain simple tests for motion and sensation provide a method of making the diagnosis of a median nerve lesion. The paralysis and marked atrophy of the small hand muscles which follow a median nerve lesion produce a striking, characteristic clinical picture. The thenar eminence becomes flattened and the metacarpophalangeal joint of the thumb stands out like a bony knob over which the skin is drawn tightly. The thumb falls back to be in the plane of the palm and as a result the typical "ape hand" is seen (Fig 3). Paralysis of the flexor sublimis and the lateral portion of the flexor profundus digitorum muscles, due to a median nerve lesion in the arm, is evidenced by an absence of flexion of the index finger and feeble flexion

of the middle finger. When the patient attempts to make a fist, the index and middle fingers flex only slightly. Paralysis of the flexor longus pollicis muscle makes it impossible for the patient to flex the distal phalanx of the thumb. Apposition and abduction of the thumb at right angles to the palm are impossible because of paralysis of the thenar muscles. It would seem impossible to mistake a median nerve lesion in the presence of these marked losses of motor function. In old cases, however, supplementary movements may have been acquired by the patient to such a degree that the closest examination leaves one



Fig. 3—Typical deformity in a median nerve lesion. Note the flattening of the thenar eminence and the tendency of the thumb to fall back into the plane of the palm.

in doubt. For example, apposition of the thumb to the little finger may be simulated by the action of the adductor pollicis combined with the inner head of the flexor brevis pollicis and flexion of the terminal phalanges of the little finger. The one movement which cannot be imitated, however, is flexion of the terminal phalanx of the index finger.

Confronted with the task of making a diagnosis of a median nerve lesion, the examiner should ask the patient to make a fist, which he cause of his inability to flex completely the index finger is unable to appose the tip of the thumb to the tip of

the little finger because of his inability to adduct the thumb. Or again the patient may be asked to clasp his hands together and one is then able to see the inability of the patient to flex the index finger on the affected side.

The area of loss of sensation to pinprick in median nerve lesions may vary from the area of complete anatomical distribution of the nerve to the isolated supply of pinprick which occupies the terminal two phalanges of the index and middle fingers but in particular the palmar surface of the terminal phalanx of the index finger. The important thing to remember is that an area of sensory loss to pinprick less than the area of anatomical distribution may not be accepted as evidence of a partial lesion, nor as a sign of recovery of function after operation. The large overlap of the radial nerve to the palm of the hand accounts in a large measure for this variation in the size of the area of sensory loss to pinprick (Fig. 4).

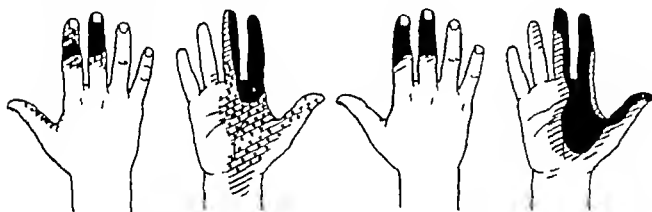


Fig. 4—Types of loss of sensation in median nerve lesions

The skin of the palm in median nerve lesions often is purplish cyanosed, red and cold, and it may be dry, chapped and scaly. Ridging and hypertrophy of the nails occur and in contrast to the normal hand the nails are pinched in at their sides so that the surface becomes more convex. Trophic ulcers occur commonly on the distal phalanx of the index finger as a result of cigarette burns (Fig. 5).

A rather large number of median nerve lesions, and not infrequently sciatic nerve injuries, may be characterized by the predominance of pain. This type of lesion was described first during the American Civil War by S. Weir Mitchell, who characterized its intensity under the name of "causalgia," a term which should be reserved for this clinical entity alone. In such cases total paralysis of the muscles below the level of the wound is rare, but some weakness in movement is always present in the flexors of the index finger and the thenar muscles.

Several cases of causalgia have been observed as a result of injuries



received during the present war and two types of causalgia are now apparent. In the one, the patient receives relief from his pain by immersing the hand in warm water and in the other type relief is obtained by immersing the hand in cold water. Oscillometric studies show that there is a marked vasoconstriction of the vessels of the

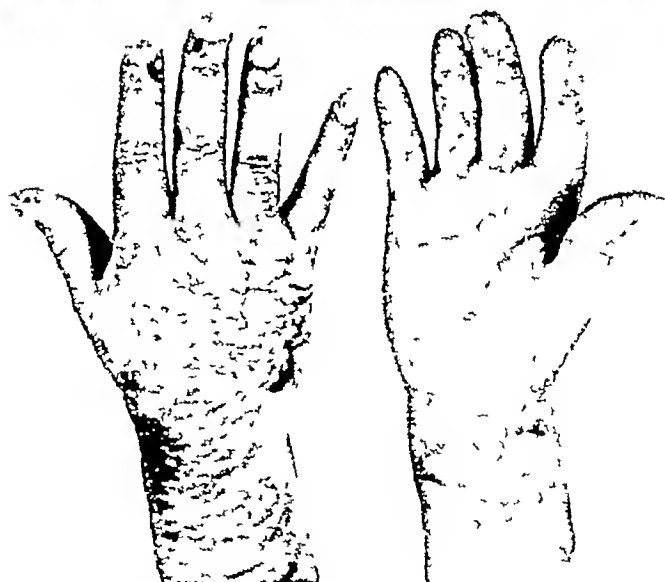
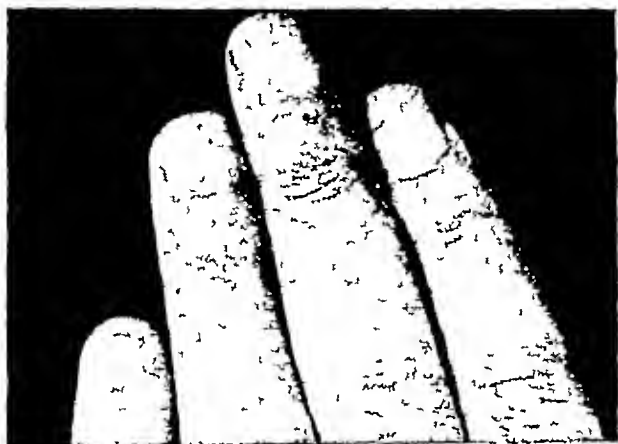


Fig 5—Nail changes and ulceration of skin in median nerve lesions

affected part in the first type while in the second group there is a vasodilatation of the vessels. It has been found that in both types of cases interruption of the sympathetic nerve supply to the affected part relieves the pain. The exact mechanism of this relief of pain is now under investigation.

## ULNAR NERVE INJURIES

Like injuries of the median nerve, ulnar paralysis produces a characteristic deformity of the hand which is very striking (Fig 6). When the lesion of the nerve is above the wrist, these patients are unable to flex the proximal or distal phalanges of the ring and little fingers, to abduct or adduct the fingers when they are extended, to adduct the thumb, to contract the flexor carpi ulnaris, and to abduct or appose the little finger. When the lesion is at the wrist, the flexor carpi ulnaris and flexor muscles of the little and ring fingers are spared. The most

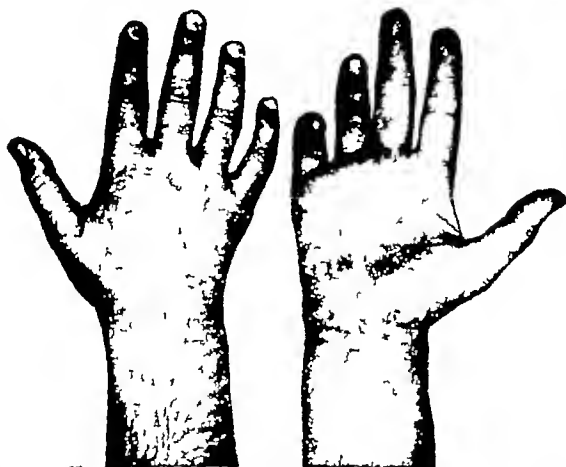


Fig 6—Atrophy of the hypothenar eminence and interosseous spaces with flexion of the little and ring fingers are typical of the deformity produced by ulnar nerve lesions.

striking symptom is the atrophy of the small hand muscles which occurs rapidly and from which recovery is slow and often doubtful. The atrophy in the first dorsal interosseous space is marked and that present in the other interosseous spaces gives the hand a skeleton-like appearance. The "clawed hand" deformity results from the unopposed action of the extensor communis digitorum, which draws the little and ring fingers into extension at the metacarpophalangeal joint, and as a result the distal phalanges become flexed. The hypothenar eminence may become so atrophied that only a thin band of tissue may be palpated.

Just a few simple tests will bring out the great loss of function which follows an ulnar nerve lesion. The patient cannot appose the little finger to the thumb, nor can he form a cone with the fingers and thumb (Fig 7). When the fist is closed the ring and little fingers may be imperfectly flexed. The patient is unable to grasp any object, such as a folded newspaper, between his thumb and index finger. When he is asked to do so and to hold it tightly, he flexes the second phalanx of the thumb vigorously and presses the tip awkwardly against the outer margin of the first phalanx of the index finger.

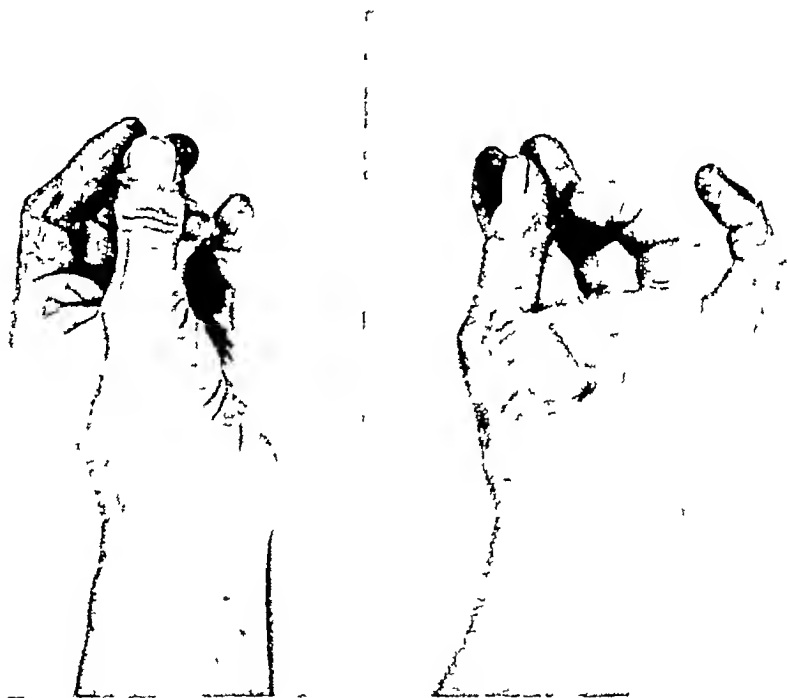


Fig 7—Inability of patient with an ulnar nerve lesion to form a cone with the fingers

(Fig 8) The patient cannot abduct and adduct the fingers with the palm of the hand flat on the table nor can he scratch the top of the table with the tip of the little finger. Just as is the case in radial and median nerve paralyses, the patient with an ulnar palsy may develop supplementary muscle movements which lead to confusion in determining the exact extent of the motor loss. For example, the extensor pollicis longus muscle is the prime mover in abduction of the thumb, and in ulnar nerve lesions it may wholly supplant the loss of the abductor muscle of the thumb. Even abduction of the fingers away from the midline may be accomplished by forcibly extending the first phalanx, particularly of the index and little fingers.

Here again examination for loss of sensation alone may make it possible to determine an ulnar nerve lesion. The most extensive loss of sensation in an ulnar nerve paralysis occupies the ulnar border of the palm, the palmar and dorsal surfaces of the little and the ulnar

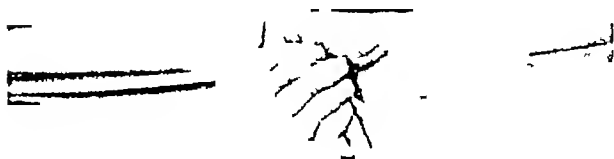


Fig 8—Inability of patient with an ulnar nerve lesion to grasp a newspaper between the thumb and index finger without vigorously flexing the second phalanx of the thumb.

half of the ring fingers (Fig 9). This is the anatomical distribution of the nerve. However, the isolated area of loss to pinprick sensation may occupy only the palmar and dorsal surfaces of the little finger and a small triangular area on the dorsal surface of the hand over the fifth metacarpal bone. It cannot be emphasized too often that the

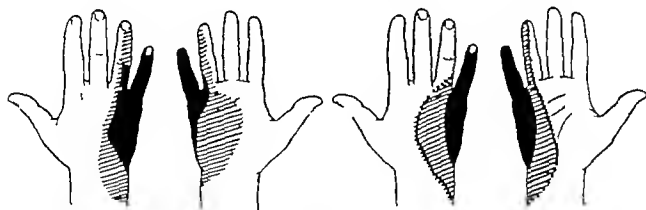


Fig 9—Types of sensory loss in ulnar nerve lesions.

rest of the area of anatomical distribution may be sensitive to pinprick because of overlap from the uninjured median and radial nerves.

As is true in median nerve lesions, trophic and vasomotor changes are well marked in ulnar nerve lesions. The little finger is usually cold dry, and a purplish discoloration is present. The little fingernail is ridged hypertrophied and deformed. It is not uncommon to find an ulceration on the tip of the little finger usually produced by a burn

## COMBINED MEDIAN-ULNAR NERVE INJURIES

In war injuries the median and ulnar nerves are frequently injured in the same patient. The deformity which follows a complete lesion of these nerves resembles an "ape" hand even more closely than does a median nerve paralysis alone. The wrist is slightly hyperextended, and the hand inclines toward the radial side. The thumb is abducted and lies in the plane of the palm of the hand while the first phalanges are extended moderately and slight passive flexion of the last two phalanges is present. Muscular atrophy is marked in the hypothenar and thenar eminences and in the dorsal interosseous spaces (Fig. 10).



Fig. 10—Note the marked atrophy of the thenar and hypothenar eminences in a patient with combined median-ulnar nerve lesion

Sensation to light touch is lost over the palmar and dorsal surfaces of all the fingers, excepting the areas supplied by the radial nerve at the ulnar border of the dorsum of the hand. The loss of sensation to pinprick varies considerably according to the degree of overlap of function from the uninjured radial and musculocutaneous nerves (Fig. 11).

Vasomotor, secretory and trophic changes in these combined injuries are similar to those found in cases of paralysis of the ulnar and median nerves alone. However, in one patient who had been shot in the arm there was an injury to the brachial artery and the skin was

cold, cyanotic, glossy and edematous while the nails were hypertrophied and deeply ridged

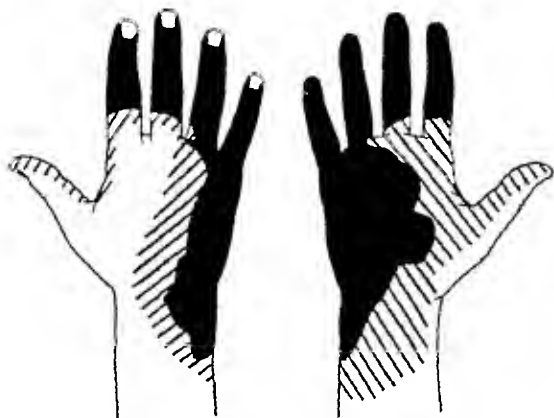


Fig. 11—Sensory loss in a combined median-ulnar nerve lesion

#### BRACHIAL PLEXUS INJURIES

When making a diagnosis of brachial plexus injuries, many of which have occurred as a result of gunshot injuries during the present war it is a common habit to attempt to group them into the classic upper brachial plexus injury described by Erb or the lower type of injury to which Klumpke's name is given. This is not difficult to do in those patients who suffer from a brachial plexus injury at birth but the levels of the lesion in individuals injured in automobile accidents, by stab or by gunshot wounds are not so easily classified. When the major paralyses produced are in the hand they resemble the paralysis described by Klumpke. In other words, the muscles paralyzed are those supplied by the ulnar and inner head of the median nerve.

It is much more helpful to the patient and to the physician if the function of each muscle in the upper extremity is examined and designated as weak or paralyzed on a chart with diagrams of the brachial plexus and the muscles supplied by each of its divisions. If this is done a classification into types not only becomes unnecessary, but its futility is fully recognized and instead the component parts of the brachial plexus are singled out for attention. Injuries of the brachial plexus as the result of stretching due to depression of the shoulder and rotation of the head and chin to the opposite side or to

direct blows to the supraclavicular area may recover spontaneously over a period of several months

### SCIATIC NERVE INJURIES

An injury of the sciatic nerve may not be classed as such if its peroneal or tibial division is injured alone in the thigh, as is frequently the case in a bullet or a shrapnel wound. When the entire sciatic trunk is injured, the deformity is unmistakable, the foot dangles and drops as the patient walks and it is brought down in a flail-like manner. All of the muscles below the knee are paralyzed, and the patient is un-

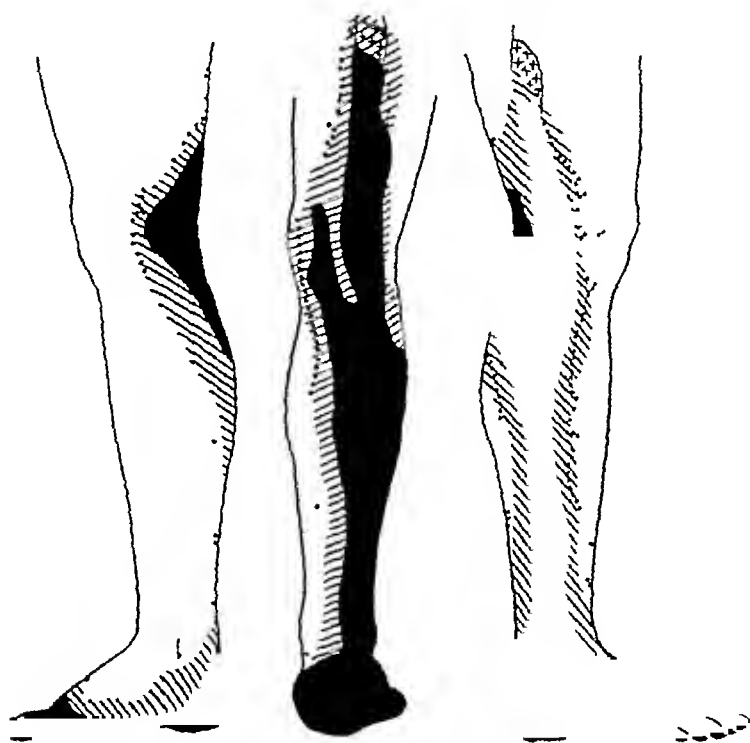


Fig 12—Sensory loss in a lesion of the sciatic nerve

able to stand on his heels or toes. The knee jerk is always present and the Achilles jerk is always absent but muscle atrophy may be masked by the edema and infiltration of the tissues of the leg. Sensation is diminished or lost over the entire foot with the exception of the inner border of the arch and the internal malleolus and the outer side of the leg to the knee. The overlap of the adjacent uninjured nerves is considerable so that the upper level of the loss of pinprick may extend only to the middle third of the leg. As was noted in the median nerve, causalgia of the sciatic nerve occurs commonly. The pain is referred to the sole and may be associated with a spasm of the

muscles of the sole of the foot. Ulcerations of the plantar surface of the foot are common, and hyperkeratosis frequently occurs so that the skin over the dorsum of the foot may be covered by scales and crust (Fig. 12)

#### PERONEAL NERVE INJURIES

The deformity produced by a peroneal nerve injury is similar to that produced in a radial nerve lesion. The footdrop which occurs is complete and is often accompanied by a slight drop of the first phalanx of all of the toes. The steppage gait is characteristic and the

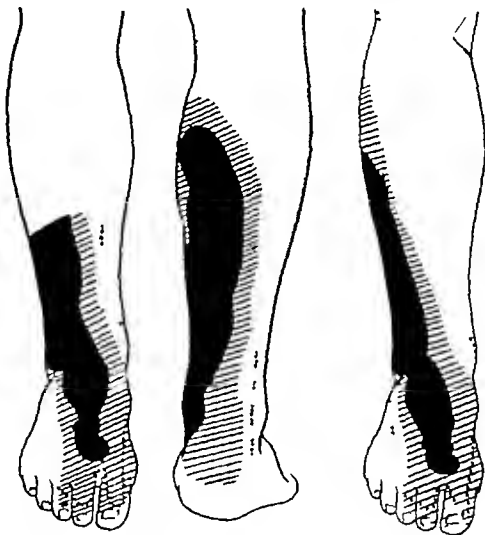


Fig. 13—Sensory loss in a peroneal nerve lesion

point of the foot is dropped and abducted. It is necessary to immobilize the knee of the patient when one examines for voluntary movement, but it is not difficult to observe that dorsiflexion of the foot and toes is impossible. Adduction of the foot may be performed by the tibialis posterior muscle, and the distal phalanges of the toes may be extended by contraction of the interosseous tendon, but abduction of the foot is impossible. It is important to remember that strong flexion of the toes may occasionally result in inversion and slight dorsiflexion of the foot by a mechanism similar to that which



produces extension of the hand in radial nerve lesions when the flexors of the fingers are strongly contracted

Sensation is lost over the dorsal surface of the foot, the anterior and lateral surfaces of the leg. In the foot sensation is lost to the base of the toes, extending outward to a point between the fourth and fifth toes and inward to the base of the first metatarsal bone. Just as in radial nerve lesions, the isolated supply to pinprick sensation may be extremely small and is usually represented by a narrow band which extends from a point a little above the junction of the lower and middle third of the outer surface of the leg, diagonally across the dorsum of the foot to a point over the middle of the metatarsal bone of the great toes (Fig 13)

### TIBIAL NERVE INJURIES

Lesions of the tibial nerve below the popliteal space are not common, and isolated lesions of the tibial division of the sciatic above that point are extremely rare. There is paralysis of plantar flexion of the

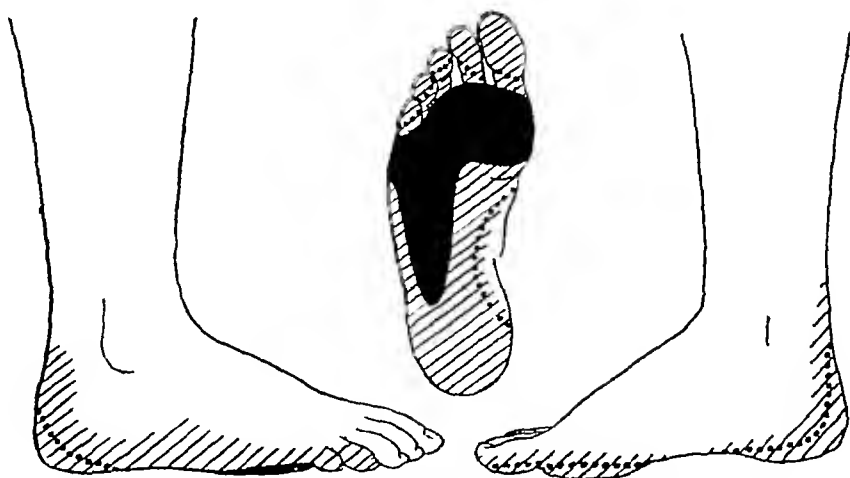


Fig 14—Sensory loss in a tibial nerve lesion

foot and true adduction of the foot is impossible. If it can be performed, it is always accompanied by elevation of the foot and then is produced by contraction of the *tibialis anterior* muscle. Flexion and separation of the toes are abolished, but the foot may be plantar flexed feebly by the *peroneus longus* muscle. Walking is difficult and the foot hangs down, is swollen, edematous and discolored.

Sensation is lost over the sole of the foot except at the inner border (Fig 14) and frequently *causalgia* may occur, particularly in incomplete lesions of the tibial nerve. Trophic ulcers of the malleoli, heel

and toes, nail changes and edema are common, and in one of our own cases an indolent ulcer of the heel was the most disturbing symptom which kept the patient from work.

#### OTHER NERVE INJURIES

The most commonly injured peripheral nerves have been mentioned, but of the remaining nerves the axillary, musculocutaneous and femoral are occasionally injured. The *axillary nerve* may be injured as the result of fracture of the head of the humerus and subglenoid dislocations. Paralysis of the deltoid muscle with loss of abduction of the arm from the side is the most characteristic symptom. Injuries of the *musculocutaneous nerve*, which innervates the biceps muscle, are rarely seen in civil life. Recently in the European Theater of Operations the opportunity was presented of observing three patients with isolated musculocutaneous injuries and the resulting paralysis of the biceps muscle. All of these injuries occurred in paratroopers and were produced by slipping of the parachute bands off the shoulder and across the upper arm so that the nerve was injured by direct pressure. The *femoral nerve* may become involved by tumors, operative wounds, psoas abscess or in the prolonged gynecologic operations in which the thighs are strongly abducted. If all the branches of the nerves are involved, the hip joint cannot be flexed and the leg cannot be extended.

#### ELECTRODIAGNOSIS

The muscles paralyzed as a result of a peripheral nerve injury react abnormally to electrical stimulation. They do not react to the faradic current and although early after injury they are hyperexcitable to the galvanic current this reaction disappears after two weeks. Then the quick reaction of the normal muscle is replaced by a slow contraction of the muscle sarcoplasm which is the only contractile tissue remaining. This is a very simple statement of the "reaction of degeneration," but it is a practical means of using a rather confusing law.

Recently, experimental work by Pollock and his associates has produced very interesting results in new methods of electrodiagnosis. By the use of currents of varying duration and strength it would appear that it will be practical to determine whether or not regeneration is occurring in a repaired peripheral nerve or whether degeneration is complete and surgical repair is indicated. The practical importance of such an electrodiagnostic method can hardly be overstated because it affords a method of determining whether regeneration of nerve fibers is occurring before any clinical evidence of return of muscle function can be detected.

## DIFFERENTIAL DIAGNOSIS

The greatest sin which can be committed is to ignore the possibilities of a peripheral nerve lesion at an early stage when repair of that nerve would mean the difference between a completely successful functional result and a failure when undertaken at a later date. The differentiation of peripheral nerve lesions from *severed tendons*, *ischemic paralysis*, or *fibrotic and inflammatory reactions* is not difficult. The combination of motor and sensory loss and the change in the reactions to electrical stimulation readily differentiates these lesions. The segmental distribution of the paralysis and dissociation of sensory loss aid in the differentiation of intramedullary spinal cord lesions, such as syringomyelia and tumors. It must be remembered that a peripheral nerve injury is a lesion of the lower motor neuron and always produces a loss of motion coupled with a loss of sensation whereas, for example, anterior poliomyelitis produces only a loss of motion.

The disturbances of motion and sensation which are found in *hysteria* never conform to the known organic symptoms which accompany specific peripheral nerve lesions. For example, a patient who received a trifling injury to the arm while at work maintained that he was unable to flex the wrist or any of his fingers. Yet, when he was asked to do so, he could appose his thumb and little finger and could grasp a piece of paper tightly between the thumb and index finger. The first movement was a test for median nerve function and the latter a test of function of the ulnar nerve. The loss of sensation in a functional lesion is likely to be glove type or may resemble some geometric figure.

As a result of injuries received during this war it may not be uncommon to encounter contractures and loss of function of the hand which occur when the site of the wound may be at a point on the body far removed from the hand. In such instances the hands will appear cold and cyanotic, the amplitude of the pulse may be diminished, perspiration may be excessive and the skin may appear macerated. This clinical entity has been designated as a *reflex nervous disturbance* and later as a *physiopathic affection*, by others it has been called "congealed hand." Carefully directed and persistent physical and psychotherapeutic treatment will result in a cure of these patients.

Severe cases have been observed as a result of gunshot injuries received in the upper extremity in the present war which have involved the *major arteries* of the extremity without direct injury to the nerve. The loss of function which has resulted, however, has been one which is difficult to differentiate clinically from an injury to the peripheral

nerve and is undoubtedly the result of a loss of function of the nerve trunk due to interruption of its blood supply. The rapid onset of muscle atrophy in these cases with the accompanying vasomotor disturbances of the skin have made the prognosis very serious.

### SURGICAL TREATMENT

**Differentiation of Anatomical and Physiological Lesions**—Having determined that a peripheral nerve lesion exists the next problem concerns its treatment. There is one important fact which must always be kept in mind and this is that there is no way by which complete anatomical and physiological interruption of a nerve trunk can be differentiated. It can be decided whether or not the loss of function is complete or incomplete and if it is incomplete anatomical division cannot be present except as a lateral notch. In the presence of a complete physiological interruption, one may say that an anatomical lesion does not exist only when subsequent examination shows some evidence of return of function. Complete paralysis of all the muscles supplied by a peripheral nerve below the level of the lesion, loss of normal electrical reactions of the muscles, extensive and rapid muscle atrophy, and loss of sensation in the area of isolated supply of the nerve may be accepted as evidence of complete interruption of nerve function.

We have had the opportunity of seeing many cases which clinically were complete interruptions of a peripheral nerve the result of injury by small pieces of fragmenting Oerlikon shells, with wounds of entrance in the skin which made it seem very definite that there was an anatomical lesion of the peripheral nerve. These nerves were explored surgically only to find that the nerve trunk had not been injured anatomically but that it had been concussed by the high velocity fragment. Obviously, these injuries would recover without operation but there is no way of determining clinically the difference between an anatomical and a physiological lesion of the nerve trunk when the symptoms are those of a complete lesion. In such instances the patient deserves and must have the advantage of a surgical exploration.

**Primary Suture**—There is one rule which should be followed religiously in the presence of a peripheral nerve lesion which requires surgery and that is that *the nerve should be repaired as early as possible*. Only in this way can one look forward with confidence to the successful return of motor and sensory function. There are, of course many factors which influence the time at which a nerve may be repaired but this is the ideal situation for which one must strive.

It has been our practice to suture a divided peripheral nerve immediately after careful surgical débridement of a wound has been carried out if the interval is not longer than six hours after receipt of the injury. We believe that any wound of the soft tissues surgically treated within six hours after its receipt can be cleansed with soap and water, necrotic and torn tissue carefully removed, the wound closed, and primary healing obtained. As the result of our experimental investigations, we believe that it is possible to close wounds primarily after careful surgical cleansing when they are received later than six hours after injury and up to twelve hours, provided that any one of the *sulfonamide powders* is introduced into the wound. It has also been found that the injection of sulfathiazole jelly into the depths of a penetrating wound immediately will prevent a development of infection when surgical cleansing and débridement are carried out as late as eighteen hours after the wound has been received and when sulfonamide powder is introduced into the wound at the time of receipt and nerve repair. From experience with the wounds of the extremities involving the nerves received by British and American soldiers during the African campaign, it was found that infected wounds which had eventually healed could be reopened and the nerve repaired at a much earlier time than has been our practice in the past. This is true because sulfonamide powders were introduced into the wound at the time of the secondary operation. It is not necessary, therefore, to wait for many months before repairing a peripheral nerve to avoid the danger of lighting up a dormant infection.

Studies of experimental gunshot wounds without the introduction of the sulfonamides and the study of the use of sulfonamides in nerve wounds made under surgical conditions have proved quite conclusively that when the sulfonamides are used in reasonable dosages in the wound they have no effect upon the regeneration and healing of the nerve fibers and of the suture line.

If there is an extensive *fracture* of the bones of the extremity accompanying the soft tissue injury it may be impossible to bring the ends of the peripheral nerve together in a satisfactory manner without delaying the operation and endangering the patient's life. In such instances the nerve ends should be secured to the tissue or, if possible, brought together so that they will not retract. The nerve ends should then be sutured together at the earliest possible date following healing of the fracture and the wound. It may be necessary in many of the cases in which there is a large destruction of tissue to cover the large defect in the soft tissue with skin grafts. Many of these cases were observed in those soldiers, both British and American, injured in the

African campaign After these skin grafts have healed, the injury of the peripheral nerve should be exposed and the repair performed

Every method at the command of the surgeon should be used to obtain an *end-to-end apposition* of a divided nerve and this should be done at the earliest possible moment There is no excuse for purposely delaying the suture of a peripheral nerve Every moment of delay is accompanied by muscle atrophy, fibrosis, and ankylosis of joints so that the effector mechanism becomes more and more difficult to rehabilitate Obviously, it will be impossible to obtain an end-to-end suture in many of the gunshot injuries of peripheral nerves which have been received in this war, so that other methods of repairing these large defects in the continuity of peripheral nerve trunks must be employed

**Nerve Grafts**—Unfortunately, the clinical results of the use of *nerve grafts* employed to repair peripheral nerve injuries received during World War I were on the whole disappointing On the other hand, exact information upon the functional results of these grafts has never been available from a study of the casualties of the American army The experimental work which was performed by Huber and his associates during the last war indicated that certain types of peripheral nerve grafts might well be successful in human beings since they were successful in experimental animals However, this large amount of clinical material was never studied completely nor was it ever possible to make follow-up studies of the patients so that for all practical purposes the contributions of this large amount of material to the progress of peripheral nerve surgery were lost.

Our experiments in animals have shown that autogenous nerve grafts, in which the graft is, as nearly as possible, the same size as the divided nerve, can be successfully performed with return of function Homogenous fresh grafts are the next best method of repairing a large loss in nerve continuity Grafts stored in alcohol or any other fixative substance are doomed to failure and no clinical evidence has ever been adduced to point to a contrary conclusion There may be some hope in the use of nerve grafts stored in saline solution or kept frozen However, under any condition the use of a fresh autogenous graft is much preferred If, for example, the median and ulnar nerves are injured with a loss of continuity which cannot be bridged by the usual method of changing the position of adjacent joints, it is preferable to sacrifice a portion of the patient's ulnar nerve and use it as an autogenous graft to repair the median nerve in order to obtain function of the index finger and the middle finger so that the patient may regain a useful hand Likewise, it would be justifiable to sacrifice

a portion of the tibial nerve to repair the peroneal nerve or the sciatic nerve, and the sacrifice of the cutaneous nerves of an extremity, particularly the larger cutaneous nerves, is wholly justifiable. The use of several segments of a small nerve to repair a defect in a larger nerve in a so-called "cable graft" would appear wholly illogical, difficult and impracticable. As far as clinical results have been reported this has proven to be true, notwithstanding experiments upon animals to the contrary.

The use of a fresh homogenous nerve graft obtained from an amputated extremity offers many more chances for success than does the use of fixed grafts. Our own experience with a portion of a sciatic nerve from an amputated extremity as a graft for an injured tibial nerve provides clinical support for the experimental evidence we have collected. There should be many opportunities at Army and Navy hospitals for confirmation of this work provided careful clinical studies are begun and are carried out over a critical period of time.

Experimentally it has been shown that the *vascularization* of the graft is most important in its function as a bridge between the divided nerve ends. Fixed graft material or dead graft material cannot be vascularized and, in our opinion, fails because of that reason. We have found that trophic ulcers do not develop when nerve ends are brought in apposition either directly or by means of either an autogenous or homogenous graft. We also believe that perhaps the most important reason for the failure of the return of function after repair of a peripheral nerve injury by the use of a graft is the fact that by the time the nerve fibers regenerate through the graft and reach the distal suture line there has been a growth of scar tissue which blocks the downgrowth of the nerve fibers into the distal segment of the nerve. It is true that this point cannot be proved conclusively in animals because of the inability to use a graft of sufficient length to be comparable to that which would be used in a human being and because nerve fibers grow much more rapidly in animals than they do in man. However, our clinical experience in two cases has shown us without any question that resection of the distal suture line (that is, the line of union between the distal end of the graft and the distal segment of the nerve), after a time sufficient for the nerve fibers to have grown down through the graft, facilitates the downgrowth of the nerve fibers into the distal segment of the nerve and the return of function.

**Time Interval between Injury and Repair as Factor in Subsequent Return of Function**—As far as the ability of the nerve fibers to regenerate is concerned, there is no time interval between the time of the injury

and the time of repair beyond which an end-to-end suture will not be successful. The time interval is dependent entirely upon the effector mechanism. It is the development of muscle atrophy, of fibrosis and ankylosis of joints, which determines whether or not there can be a successful return of function after a peripheral nerve suture. Therefore, it is important to keep the muscles and joints of the extremity as mobile and in as good tone as is possible by physical therapy methods. Passive movements of the joints, massage, and proper splinting of the dependent parts of the paralyzed extremity are extremely important. They are also important after the peripheral nerve has been sutured and during the period of regeneration.

**Suture Materials**—There has been a great deal of discussion about the method by which peripheral nerves should be sutured. It can be said simply and directly that the nerve ends should be apposed by the finest suture material obtainable which will give the smallest amount of tissue reaction. We have at various times in our experimental work used human hair, tantalum wire and other suture materials, but we have found that unbraided strands of the finest black, twisted silk answers the requirements most accurately. The suture must never be placed through the body of the nerve but should only bring together the epineural sheaths.

**Criteria of Regeneration after Repair**—Finally, the same care in the examination of motor and sensory function as is used in diagnosis must be observed in attempts to determine recovery. When there is return of pinprick sensation in the isolated area of sensory supply of the nerve, regeneration of the repaired nerve ends may be said to have occurred, but only then. Likewise when there has been a return of muscle movement innervated solely by the involved nerve, regeneration may be judged to have occurred. Failure to adhere to these strict requirements has made many reports in the literature of recovery of function after nerve repair practically valueless.



# THE ORGANIC ORIGIN OF APPARENT FUNCTIONAL NERVOUS DISEASE

LEROY H SLOAN, M D \*

## CASE I

Our first patient, a white male aged 45 years, was first seen in January complaining of weakness, easy perspiration, loss of a slight amount of weight, *ready flushing*, hot flashes, restlessness and tremor of the hands together with palpitation of the heart. This symptom complex was not constant but came in attacks or *waves*. During such waves the patient was compelled to sit down. After resting for a few minutes the symptoms and signs would disappear and the patient would return to his duties. On some days the spells were frequent while on others they came only occasionally. There was loss of weight, loss of appetite, increasing *frequency of bowel movement*, moderate vertigo and insomnia.

The patient had always lived with his mother. He had never married. He had never been able to mix well with people and as a result had isolated himself from practically all social contacts and given himself over to the care of his mother. The mother died during the preceding April. Some three or four months afterward the above train of symptoms put in their appearance.

Several clinical syndromes come to mind. Does the patient have hyperthyroidism? While the symptoms suggest such a diagnosis, the wavelike character of the cycle does not. Also, the basal metabolic rates which were taken many times were extremely labile—one day up and the next down, inconsistent and not dependable. The pulse during the attacks would be rapid and at rest, afterward, would be normal. It was our impression that the patient did not have either a toxic adenoma or hyperplastic thyroid to account for his difficulties. There was no palpable enlargement of the thyroid at any examination.

A second clinical syndrome for passing consideration is the currently popular male climacteric. This patient had to all ordinary study no evidence of a male menopausal status. True, he had never experienced any real sexual urge but his present gonadal status varied little from that of his past years.

---

From the Illinois Central Hospital, Chicago

\* Professor of Medicine, University of Illinois School of Medicine, Director of the Medical Service, Illinois Central Hospital, Adjunct Staff, St. Luke's Hospital

A third syndrome suggested by the easy palpitation, flushing, rapid alteration in pulse rate, variation in blood pressure, and weakness, was postural hypotension. But here again there was no finding to clinch such a thought. The pressure, while very labile, did not conform to the pattern of postural drop.

The syndrome of hyperirritable carotid sinus could not be confirmed.

During the period of the last war this case would undoubtedly have been labeled as neurocardiac asthenia or effort syndrome. Blushing, flushing, sweating, palpitation, nervousness, tremor, irritability, apprehension and loss of confidence with labile blood pressure and more labile pulse—what more could be needed?

During his first sojourn in the hospital there was relatively little change in his status. He continued to be a very apprehensive, easily irritated, anxious type constantly interrogating all who came near him and at all times asking questions about his physical and laboratory findings, his future status in his work, and in society in general. Several capable internists saw him from time to time and all came to the same conclusion—that this patient aside from a mess of infected teeth was suffering from a functional condition conforming more to an anxiety neurosis than to any other syndrome or classification. This impression was confirmed by psychiatric consultation. So our patient was discharged from the hospital with the advice to have his teeth cared for, to keep with other people, to obtain and consume a generally nutritious and balanced diet, to engage in the usual and currently considered normal functions of existence, and to report from time to time for further study and check up.

The patient returned in November almost eleven months after his initial admission to the hospital. About six months after his previous discharge he first began to have pain in the left arm. He had gained a little weight prior to this time, had received attention to his teeth with the extraction of most, had thought that he was fairly well. His failure to gain much weight he attributed to his inability to procure sufficient food because he still lived alone, still ate wherever he happened to be. His friends had been very cooperative and his employers more than kind. A much easier job had been assigned to him. On examination in November the patient showed all of the symptoms and signs mentioned above—the waves of flushing, of sweating, of palpitation, and so forth—but—there was beginning *atrophy* of the small muscles of the hand, there was numbness of the small and ring fingers and the *complaint of pain* which began in the arm, advanced to the left shoulder and subscapular area and into the cubital space.

In the supraclavicular area on the left there was a small gland. This gland was removed and microscopic examination showed it to be metastatic adenocarcinoma. Here then was the organic origin of our patient's difficulties. Away went the anxiety neurosis, away the cardiac asthenia, away the male climacteric.

The blood pressure remained the same, the heart rate the same, the weight decreased, atrophy advanced, pain became much more severe, more glands appeared. The blood Wassermann and Kahn tests were, as one might expect, entirely negative and the spinal fluid showed no block. It was clear, with only six cells and 29 mg of total protein, a negative Wassermann reaction and a flat gold chloride curve. When the carcinomatous gland was found, repeat x-rays of the lung and chest cage were made. In the apex of the left upper lobe was an increased soft tissue density. A classical Horner's syndrome made its appearance on the left with enophthalmos, miosis, ptosis. Gradually the pain spread to the right side. Roentgen therapy was given to the area of the left supraclavicular fossa, cervical vertebrae, and the lung. There was a consistently downward course and the patient expired *sixteen months* after his initial complaints. Autopsy showed an adenocarcinoma involving the apex of the left lung, the left cervical and supraclavicular soft tissues, the cervical fifth, sixth and seventh and the first dorsal vertebrae.

## CASE II

Our second patient was a clerical worker 57 years of age who had been under treatment in the outpatient department at irregular intervals. The history obtained therein was chiefly of pain in the right shoulder and right arm. This pain had come on following a night of bowling after which he went out into zero weather before he had had an opportunity to cool off. The next morning he developed sharp pain beneath the right shoulder blade. The pain was quite constant and not affected by any motion of the shoulder, the elbow, the wrist or the neck. The pain was worse in cold weather, much worse in very cold weather, relieved in part by heat, either moist or dry, very slightly relieved by salicylates and similar antineuralgic medication. The patient insisted that the pain was now limited to a small area of the arm and elbow region, appeared to originate above the clavicle but was most marked at or near the elbow. From February on the difficulty persisted until he became extremely nervous and took to heavy drinking to relieve the distress. All laboratory examinations were negative except for a slight clouding of the right apex of the

lung which was interpreted after much discussion as probably tuberculosis of minimal extent.

The patient became increasingly difficult to manage, increased the length of his alcoholic sprees, refused hospitalization, became more and more apprehensive but, apart from the slight clouding of the right apex, showed no single pathological or clinical finding of any moment. He was therefore regarded as a high grade psychoneurotic patient with an anxiety state. The alcoholic factor was given due consideration and felt to be just one more added factor in the clinical picture and perhaps the important one. However, he was given a few injections of sodium salicylate and iodide of sodium intravenously.

Radiant heat was advised and administered to him at irregular intervals along with medication by mouth and the usual topical applications for nonspecific neuralgic pain. However, in the minds of all who contacted him there was the settled feeling that here was a high grade psychoneurotic patient trading on a functional difficulty and bathing his depressed spirits in alcoholic libations far and beyond the therapeutic dosage.

In October he finally came into the hospital. Ten days before this admission he had developed pain across the right chest from the midline and referred up to the arm and the muscles of the neck. General examination at this time was again negative. The laboratory examinations were normal throughout. There was no pain of any sort on any motion of the shoulder, elbow, wrist, neck or body. Yet the patient complained bitterly of pain down the right arm and especially along the medial border of the triceps and ulnar border of the lower arm.

Of great importance to all of us should be the continued complaint of the patient of pain in one general area, in this instance in the right arm, shoulder and neck. This insistence points to an organic lesion and not to a functional one. In the functional patient other areas are sooner or later incriminated. Rarely does he stick to one portion of his anatomy. The paucity of physical findings may be present in both. Why did we regard the patient as a psychoneurotic? Chiefly I expect because we could find no other explanation for his distress. Here was a patient who had been divorced, who had a background of unhappiness as the soil for his anxiety state, who had taken to alcohol to cure his difficulties and who continued to *bowl right* along even up to the time when he came into the hospital. His stubborn and uncooperative nature just added that much more evidence that our patient was suffering from a functional state.

But, let us follow him a bit longer. Within a few days after admis-

sion to the hospital the lesion in the apex of the right lung had spread until there was now an area of opacity very suggestive not of tuberculosis, not of an apical cap, but of malignancy. Here, then, was the organic basis for his supposedly functional state. Shortly after this the patient began to show atrophy of the muscles of the lower right arm and hand, the right pupil became smaller than the left, the palpebral fissure narrowed and the bulb retracted—all indicating a Horner's syndrome produced by compression or infiltration of the tissues of the sympathetic system.

This patient began to have symptoms after bowling for several hours and then going out into the bitter cold—a perfect setting for a refrigeration neuralgia or neuritis or whatever one might wish to call it. But, the lesion in the right apex spread, involved the cervical vertebrae, compressed the brachial plexus, comprised the esophagus and the trachea, finally led to a paralysis of peripheral type of the entire right arm with glossy skin, atrophy and weakness.

The patient terminated his earthly sojourn *eighteen months* after his initial complaint. For exactly a year from the time of his first complaint there were no demonstrable bony changes even of minor degree. Now what was found at autopsy on this patient? A carcinoma of the apex of the right lung beginning in the bronchial structures and extending into the superior sulcus area, invading the ribs, the cervical vertebrae, and the soft structures at the base of the neck on the right side.

In my experience the tumors of the apex of the lung have been more often on the right side, have produced pain at some stage in their course, and have originated in the great majority of instances in the bronchial tissues and not in the tissues of the nervous system. In other words, superior sulcus tumors are usually bronchogenic carcinomas.

#### SUMMARY

We have presented as examples two patients both regarded as suffering from functional nervous disease over a period of weeks and months. Both were shown on further examination to have tumors of the lung, one in the right apex and the other in the left apex. Both were examined by competent internists and neurologists. The one exhibited many of the symptoms and signs seen in panic reactions of anxiety neurosis, the other, consistent pain in the right arm. One lived *sixteen months* and the other *eighteen months* after the initial complaints began. Both were shown at autopsy to have sufficient organic, neoplastic disease to explain all of the symptoms presented throughout the long course of their illnesses.

The consistent segmental distribution of pain is assumed to be of organic origin until proved by long observation not so to be. Pain in the upper chest or arm associated with slight percussion dullness over the apex and linked with a history of even slight hemoptysis is highly suggestive of apical carcinoma. Persisting pain in the arm with atrophy or weakness or numbness of the extremity calls for x-ray study of the apical portions of the lung. A palpable gland in the supra-clavicular area should be removed for microscopic study.

Most of the apical tumors giving the above symptoms and signs have been shown at autopsy to be bronchogenic carcinomas. Occasionally, as in one seen previous to the case described and showing much the same clinical picture, they are from nervous tissue of the sympathetic system.

# BENIGN LYMPHOCYTIC CHORIOMENINGITIS

LOREN WILLIAM AVERY, M D \*

## PRESENTATION OF CASES

As a basis for discussion of lymphocytic choriomeningitis the following clinical cases are presented

CASE I—F B, a white male of 17 years, was admitted to Presbyterian Hospital, Chicago, in March, 1935. He had been well up to fourteen days prior to admission. At that time, both he and his younger brother suffered from a mild upper respiratory disorder characterized by slight elevation of the temperature, headache, nasal discharge and general malaise. These symptoms lasted for about a week after which time both patients appeared to have recovered. In a few days, however, the older brother became ill complaining of throbbing headache, photophobia and stiffness of the neck. He again had a slight elevation of temperature and a purulent nasal discharge. He was not severely ill and was able to travel a distance of fifteen miles to consult his physician for local treatment of the nasal condition. Four days before admission to the hospital the above symptoms increased in severity and vomiting was present.

Upon examination the patient was alert, lying quietly in bed shading his eyes from the light. He was able to give an accurate and complete description of the details of his illness. The neck was rigid and painful to pressure. The Kernig sign was bilaterally present. The deep and superficial reflexes were present and equal on the two sides. The plantar reflexes were of the flexor type. There was no disturbance of sensation or coordination.

The temperature was 100.8° F. The pulse ranged from 66 to 88. The leukocyte count was 15,000, being predominantly polymorphonuclear in character. There were 4.6 million red blood cells. The hemoglobin was 90 per cent. The urine was negative.

The spinal fluid was clear. The pressure was 105 mm. It contained 440 cells per cubic millimeter, 44 per cent of which were mononuclear lymphocytes, 56 per cent were polymorphonuclears. The Nonne and Ross-Jones reactions were positive. The total protein was 36 mg per 100 cc. The gold curve was 1111221100. The sugar was 54 mg per 100 cc. The Wassermann reaction was negative. The spinal

---

From the Neurological Department, Presbyterian Hospital, Chicago

\* Associate Professor of Neurology (Rush), University of Illinois College of Medicine, Associate Attending Neurologist, Presbyterian Hospital

fluid was found to be sterile on culture and no organisms were found on direct smear

The patient improved quickly following the initial spinal puncture. The temperature returned to normal. The spinal fluid twenty-four hours after admission contained 280 cells of which 50 per cent were mononuclear lymphocytes. Four days after admission 90 cells were found in the spinal fluid. These were all lymphocytes. The patient was dismissed twelve days after the onset, being entirely free from all symptoms.

CASE II—G. H., a white boy of 8 years, fourteen days before observation suffered a typical attack of measles without any complications. Two days before he was seen his mother noticed that he was apparently ill. He had a temperature of  $100.2^{\circ}$  F., complained of headache, soreness and stiffness of the neck, and refused to eat. Vomiting occurred.

Upon examination in his home, it was found that the lad was not severely ill. He was in bed and was playing with his toys. The neck was distinctly rigid. The Kernig sign was slightly positive. The temperature was  $99.8^{\circ}$  F. There were no evidences of cranial nerve involvement, and motor power, sensation and coordination were found to be normal. The reflexes and optic fundi were normal.

The spinal puncture was performed at the home. The fluid was clear, and the pressure was 180 mm. Ninety cells were present, all of which were lymphocytes. The Nonne and Ross-Jones reactions were positive. The colloidal gold test gave a suggestive meningeal curve. The Wassermann reaction was negative. The sugar was 60 mg. per 100 cc. The fluid was sterile on culture and no organisms were found on direct smear.

The clinical symptoms rapidly disappeared so that within seventy-two hours the boy felt and appeared well.

CASE III—G. W., a white male of 54 years, was admitted to Cook County Hospital in April 1932. He was a vagabond. The subjective history indicated that a week before admission he had a slight chill and began to have severe headache and stiffness of the neck as well as general malaise. Two days later he complained of double vision. Nausea and vomiting were present.

Upon examination on admission it was found that the pupils were equal and reacted to light and convergence. There was no evidence of paralysis of the extrinsic ocular muscles and subjectively the diplopia had disappeared. The optic fundi showed slight blurring of the disks but no swelling was present. There was no evidence of paralysis of the skeletal muscles. The reflexes were equal on the two sides and generally brisk. The plantar reflexes were normal. There was no disturbance of sensation or coordination. The neck was rigid, and the



Kernig and Brudzinski signs were positive. The patient appeared ill. The temperature was 102.4° F. Herpes were present on the lips, and the tongue was dry and coated.

The blood showed a polymorphonuclear leukocytosis of 12,000, and there were 3.9 million red cells. The hemoglobin was 70 per cent. The blood Wassermann reaction was negative. The spinal fluid pressure was not taken, but the fluid was clear and colorless. Six hundred and eighty cells were reported in the spinal fluid, 75 per cent of which were mononuclear lymphocytes. The Pandy reaction was moderately positive. The protein was 100 mg per 100 cc. The colloidal gold curve was 0112222100. The sugar content was 67 mg per 100 cc. The Wassermann reaction was negative. On culture the spinal fluid was sterile and no organisms were found on direct smear of the sediment which formed in the fluid.

The patient continued to be rather ill for two weeks. There was an afternoon elevation of temperature from 101° to 102° F. During this time the headache and stiffness of the neck persisted. A gradual improvement began after the fourteenth day but it was not until the sixth week after onset that the symptoms entirely disappeared. Repeated spinal punctures during the time the patient was in the hospital showed varying degrees of pleocytosis of the fluid which had the tendency to decrease gradually as the clinical picture improved. He was discharged nine weeks after admission.

CASE IV—L. S., a white male of 32 years, was admitted to Presbyterian Hospital, Chicago, in May 1936. He had been well up to fourteen days previous to admission. At that time he suffered from a mild upper respiratory disorder characterized by a slight elevation of temperature and slight nasal discharge and frontal headache. Eight days before admission he complained of weakness and soreness of the neck and back. The day before admission he complained of severe frontal headache, slight nausea, stiffness and pain in the neck.

Upon examination it was found that the neck was rigid and painful to motion. The Kernig sign was bilaterally present. The deep and superficial reflexes were present and equal on the two sides.

The temperature was 101° F. The pulse ranged from 72 to 84. The leukocyte count was 12,900 and was predominantly polymorphonuclear in character. There were 4.4 million red blood cells, and the hemoglobin was 84 per cent. The urine was negative.

The spinal fluid pressure was elevated and the fluid was clear. It contained 410 cells per cubic millimeter, all of which were lymphocytes. The Nonne and Ross-Jones reactions were positive. The total protein was 104 mg and the sugar was 45 mg per 100 cc. The gold curve was 0012332300. The Wassermann reaction was negative.

A subsequent spinal puncture two days later showed 390 lymphocytes. The Nonne and Ross-Jones reactions were negative. The total

protein was 87.7 mg. The sugar was 62.7 mg. The gold curve was 1122221100. Bacteriological examinations of both samples of spinal fluid revealed no organisms.

A third spinal puncture done a week after admission revealed 86 lymphocytes.

Recovery was somewhat slow especially in regard to nausea and vomiting. This, however, may have been more referable to a duodenal ulcer than to the meningitis. At the end of two weeks the patient was free from all symptoms of the disorder. He has remained well and no sequelae have been observed.

#### COMMENT

The above cases all have certain features in common. Their onset was relatively sudden following some mild infectious disorder. They all occurred in the spring. The clinical symptoms in all the cases were those of meningitis. In all, the pleocytosis of the spinal fluid was preponderantly lymphocytic in character though in Case I there was an early preponderance of polymorphonuclears. In all the cases the spinal fluid was sterile, the sugar content was normal and the globulin was slightly increased. Recovery occurred in all the cases.

**Diagnosis**—It is evident that these clinical syndromes belong to types of meningitis characterized by lymphocytes in the spinal fluid. They must be differentiated from tuberculous meningitis. The mild course of the disorder, the failure to find tubercle bacillus and the normal sugar contents of the spinal fluid definitely indicate that they are not tuberculous meningitis. Syphilitic meningitis, which is also characterized by a lymphocytic pleocytosis, needs a little consideration. The finding of consistent negative Wassermann reactions of the spinal fluid, which at the same time shows evidence of an active inflammatory reaction, is entirely incompatible with a syphilitic infection. Other conditions which produce a lymphocytic pleocytosis such as poliomyelitis and epidemic encephalitis would hardly need to be considered except, perhaps, in Case II in which the pleocytosis was below 100.

These cases all belong to a benign form of meningitis which, in the past, would have been classified as aseptic or serous meningitis. Because of the preponderance of lymphocytes in the spinal fluid they have more recently been classified as *benign lymphocytic meningitis*.

#### THE BENIGN LYMPHOCYTIC MENINGITIC SYNDROME

During the past decade benign forms of lymphocytic meningitis have attracted considerable interest. While such clinical syndromes have been encountered for many years there had been no unanimity of opinion as to their identity and considerable confusion has always

existed as to their pathogenesis. The earlier conception of these disorders was that they represented the meningeal reaction to acute infectious diseases, acute intoxications or trauma. It has been known for years that in the beginning of many of the acute febrile conditions, especially in childhood, a lymphocytic pleocytosis may be present in the spinal fluid associated with an increase in the volume of spinal fluid with resulting increase in pressure. These syndromes were classified as serous meningitis.

Beginning in 1925 considerable interest was stimulated in reference to this syndrome by the rather frequent reports of sporadic and epidemic instances of a benign type of meningitis. These reports came chiefly from Europe but instances were also reported in America. Wallgren<sup>1</sup> reported an epidemic which he called "meningitis aseptica acuta." From scattered areas in Europe several reports were made and the diseases were designated as "acute benign idiopathic serous meningitis,"<sup>2</sup> "benign aseptic purulent meningitis"<sup>3</sup> and "epidemic meningitis serosa."<sup>4</sup> In this country the designation was "benign lymphocytic meningitis."<sup>5</sup>

A review of the reported cases indicates that they were all clinically similar. The onset was usually sudden and very frequently associated with some respiratory disorder. The meningitic syndrome was usually rather mild but had the cardinal characteristics of meningitis. These pertinent data were always obtained from the spinal fluid. The fluid was clear and under slightly elevated pressure. There was always an increase in cells ranging from 30 to 1500 or more. This pleocytosis was preponderantly mononuclear lymphocytic in character. However, polymorphonuclear cells were observed, though usually not more than to the extent of 40 per cent. It is interesting that in the early days of the disorder the polymorphonuclear cells were more frequently observed than in the later stages. Instances have been observed in which the identical clinical picture was associated with preponderantly polymorphonuclear pleocytosis during the entire course of the disorder. However, the most characteristic pleocytosis was of the lymphocytic type. The sugar and chloride contents were always normal. The protein content was slightly elevated. No organisms were found in the spinal fluid either by direct smear or culture. The clinical course of the cases was always comparatively mild, lasting from days to months, and recovery always took place. Sequelae were thought to be absent.

**Etiology**—There was considerable agreement among the various authors that these disorders were due to a filtrable virus. Some suggested that it was an attenuated form of tuberculous meningitis. This

latter concept failed to arouse interest because of the lack of all confirmatory evidence. While most observers believed that it belonged to the virus group of disorders there was a considerable disagreement as to the identity of the virus. Some observers believed it to be related to poliomyelitis while others considered it to be a form of epidemic encephalitis.

These discussions, as to the relationship of this disorder to other virus diseases, were largely terminated in 1935 by the report of Rivers and Scott,<sup>6</sup> who were able to recover a filtrable virus from the spinal fluid in typical clinical cases. This virus was capable of producing in laboratory animals a constant type of lymphocytic infiltration on the meninges and choroid plexus.

With the recognition of the virus and the study of the resulting pathologic changes as seen in the experimental animal, the term "lymphocytic meningitis" has been replaced by or held to be synonymous with *lymphocytic choriomeningitis*. The virus is designated as the choriomeningitic virus.

Further investigations on the pathogenic role of this virus have revealed several interesting facts. There has been no proven instance in which one patient has contracted the disease from another. This has suggested that there is an animal reservoir for the virus.<sup>7</sup> In six proven instances of this disorder the virus of choriomeningitis was recovered from gray mice trapped in the homes of five of the patients. Also mice trapped in the homes where infected animals had been known to exist were found to have a high percentage of immunity to the virus. Several cases have also been observed among laboratory workers handling infected mice. Even though other animals are susceptible to the virus, it would appear that one of the sources of transmission is by the way of the mouse.

The cases are seasonally distributed, being most prevalent in the spring. The frequent association of choriomeningitis with respiratory symptoms would indicate that the mode of the infection is through the respiratory tract. The virus is most readily recovered from the spinal fluid or blood taken either at the height of or before the attack. It has, at times, been isolated from the nasal discharges and from the urine. Protecting antibodies can usually be demonstrated in the blood at the end of six to ten weeks and may persist indefinitely.

**Clinical Picture**—The clinical expression of infection with the choriomeningitic virus is known to be varied. There is a non-nervous type which has many of the characteristics of the "grippe." Clinical evidence of lymphocytic meningitis has been seen in epidemics of gastrointestinal disorders. Besides the classical form of meningeal involve-

ment, cases showing evidence of encephalitis have been seen. Other cases have been described in which the syndrome corresponds to that of meningoencephalomyelitis. Two fatal cases of hemorrhagic encephalitis have been reported by Howard<sup>9</sup>

It is evident that the choriomeningitis virus may produce widespread changes in the body. It seems also to be true that in its nervous manifestations it may produce different clinical and pathologic syndromes. This is in keeping with other types of filtrable virus. The virus of poliomyelitis, at times, produces polioencephalitis and the clinical syndrome in the abortive nonparalytic cases corresponds somewhat to choriomeningitis. The viruses responsible for measles, whooping cough and mumps presumably produce the syndromes of meningitis, encephalitis or meningoencephalomyelitis referable to those diseases.

The usual clinical picture is that of a mild meningitis, having a more or less sudden onset during or following symptoms of a mild upper respiratory disorder. General malaise, headache, fever and stiffness of the neck are always present. Vomiting is frequent but not constant. As a whole, evidences of cranial nerve involvement are insignificant, though blurring of the optic disk is frequently reported.

**Spinal Fluid Changes**—The changes in the spinal fluid are confined to the cells, the globulin and pressure. The sugar and chloride contents are normal. The gold curve is not significant. The Wassermann reaction is invariably negative and the fluid is sterile. The cells vary greatly in number. However, in the proven cases the cell count was always high. Armstrong<sup>7</sup> states that a clear spinal fluid with a cell count of over 1200 points to choriomeningitis. The consensus seems to be that the cell count may vary from 30 to 1500 or more.

**Course**—The course is usually mild, and it may last for only a few days. More severe cases continue for weeks and some for months. Recovery is the rule and, with the exception of the cases reported by Silcott and Neuberger,<sup>8</sup> no deaths have occurred. Sequelae have not been observed, which differentiates this disease from epidemic lethargic encephalitis.

**Pathology**—Pathologic reports concerning the changes present in proven cases of lymphocytic choriomeningitis are lacking. There is a report by Howard<sup>9</sup> containing evidence that the virus may be responsible for cases of hemorrhagic encephalitis.

Silcott and Neuberger<sup>8</sup> have reported the histopathologic findings from three cases which had the cardinal manifestations of acute lymphocytic choriomeningitis. Their findings would indicate that besides the meningitic changes, moderately severe encephalitis may be present

in the interbrain. Because these cases were fatal and the cause not proved by virus studies it is not clear that they were due to the virus of choriomeningitis.

### CONCLUSION

Some clarification is necessary concerning the concept of lymphocytic choriomeningitis. The term signifies a lymphocytic inflammation of the choroid plexus and meninges. A histopathologic diagnosis is being applied to a clinical syndrome in which meager, if any, valid pathologic observations have been made. This has come about because the virus recovered from the spinal fluid in some cases consistently produces a choriomeningitis in experimental animals. In designating all cases of benign lymphocytic meningitis as lymphocytic choriomeningitis one is assuming that all cases are due to the specific virus. There is evidence that the cardinal clinical manifestations of lymphocytic choriomeningitis can be associated with or follow such disorders as measles, mumps, chickenpox or other virus disorders. The second case reported here was presumably referable to measles. Mackay<sup>10</sup> has observed a lad of 16 years who presented the classical clinical symptoms and spinal fluid findings of lymphocytic choriomeningitis during the course of mumps. More convincing perhaps, is the report of Armstrong<sup>11</sup>. In a typical instance of lymphocytic choriomeningitis he recovered the virus of herpes simplex from the spinal fluid and was able to fulfill the usual criteria to establish its etiologic role.

In the light of our present knowledge it seems premature to regard benign lymphocytic meningitis as always being due to the choriomeningitic virus. While it is probably true that the most frequent cause of benign lymphocytic meningitis is the specific virus, it should be borne in mind that the classical clinical syndrome can be produced by other pathogenic agents.

### BIBLIOGRAPHY

1. Wallgren, A. Eine eigenartige Form von epidemischer Meningitis. *Wien. Arch f inn. Med.*, 12:297, 1926.
2. Andersen S and Wulff F. Meningitis acuta serosa idiopathica benigna. *Ugesk f laeger* 92:572, 1930.
3. Schuff E. Ueber gutartige aseptische eitrige Meningitis im Kindesalter. *Monatschr f Kinderh.*, 48:434, 1930.
4. Eckstein, A. Epidemische Meningitis serosa. *Klin Wchnschr.*, 10:22, 1931.
5. Viets, H. R. and Watts, J. Aseptic (Lymphocytic) Meningitis. *J.A.M.A.* 93:1553, 1929.
6. Rivers, T. M. and Scott, T. F. M. Meningitis in Man Caused by a Filtrable Virus. *Science*, 81:439, 1935.
7. Armstrong C. Studies on Choriomeningitis and Poliomyelitis. *Bull. New York Acad. Med.*, 17:295, 1941.

- 8 Silcott, W L and Neuberger, K Acute Lymphocytic Choriomeningitis  
Report of 3 Cases of Histopathologic Findings *Am J M Sc*, 200 253,  
1940
- 9 Howard, M E Infection with Virus of Choriomeningitis in Man *Yale J  
Biol & Med.*, 13 161, 1940
- 10 Mackay, R P Personal communication
- 11 Armstrong, C Herpes Simplex Virus Recovered from the Spinal Fluid of a  
Suspected Case of a Lymphocytic Choriomeningitis *W Pub Health Rep.*,  
85 16, 1943

# **PATHOLOGIC PYRAMIDAL TRACT SIGNS**

## **Elicitation, Interpretation and Evaluation**

**VICTOR L. GONDA M.D.\***

### **GENERAL CONSIDERATIONS**

In determining why many errors occur in the elicitation and interpretation of some of the important neurologic reflexes, I have come to the conclusion that the textbooks on neurology and neurologic examination do not give an adequate description of this phase of the examination, especially for the beginner. Generally, the information for use in detecting the normal reflexes is satisfactory, but each book describes the techniques somewhat differently and with rather inadequate instructions for eliciting the pathologic signs. The photographs usually are not pertinent and almost invariably show only the end result, omitting a satisfactory illustration of the most important part of the technic.

The interpretation of the elicited reflexes frequently varies, even in the examination of the same patient by different neurologists. This occurs most commonly in patients with a diseased pyramidal tract. Vascular accidents, tumors, syphilis and multiple sclerosis are among the most frequently encountered diseases of the nervous system. The pyramidal pathway is involved in a large number of these cases.

**Origin and Course of the Pyramidal Tract**—At the present time it is generally accepted that the pyramidal tract has its origin in the precentral convolution (motor area), which coincides structurally with the area of the pyramidal cells, and in the region just in front of it (premotor area). There is a narrow zone (strip region) between these two areas which is of great importance in neurophysiologic research. Circumscribed lesions of any of these areas produce varying manifestations. Because the origins of the different pyramidal pathways lie in juxtaposition in the cortex and after leaving the cortex their anatomic relationship becomes closer, any disease in the pyramidal tract almost always simultaneously involves the whole system. Therefore the resulting signs, at least for general purposes, have to be considered at the present time as characteristic of pyramidal tract lesion.

Many of the fibers originating from the motor cells are very long

---

Clinical Professor of Neurology, Loyola University School of Medicine  
Attending Staff Neurologist, Cook County Hospital, Senior Attending Neurologist, Mercy and Alexian Brothers Hospitals, Chicago



some almost as much as one third of the whole body length. It is little wonder, then, that these fibers are exposed to many pathologic changes. The pyramidal fibers, also called corticospinal, upper motor, central or supranuclear neurons, after decussating at the lower border of the medulla oblongata, end around the anterior horn cells on the opposite side of the spinal cord. Hence injuries above the decussation involve the opposite side of the body, and below the decussation involvement of the pyramidal fibers causes homolateral symptoms. Regardless of the point of injury of the corticospinal neurons, the resulting symptoms are the same.

We do not consider in this discussion those fibers which decussate in the midbrain, pons or medulla oblongata.

**Results of Pyramid Tract Lesions**—The pyramidal tract is regarded as the chief executive organ in the performance of voluntary movements. A lesion of these pathways causes weakness of volitional movements and not of individual muscles. The resulting paralysis is rarely permanently complete and always affects diffuse muscular groups.

Involvement of the pyramidal system will lead to changes in the regular muscular tone, resulting in hypertonicity in the form of spasticity. It must be remembered that the limbs are flaccid in the early stages of sudden paralysis caused by involvement of the pyramidal system, and in exceptional cases of permanent hemiplegia.

**Changes in Reflexes**—Disease of the pyramidal fibers also causes some important changes in the reflexes, namely

- 1 *Increase of the deep* (generally called tendon) *reflexes*, e.g., biceps, triceps, radioperiosteal (also called supinator), knee, ankle and jaw jerk. In some cases ankle, patellar and wrist clonus can be elicited as a sign of pyramidal tract disease. However, clonus may also be present in connection with general "reflex irritability," in which case it is less regular in amplitude and rate. There is no standard as to what constitutes a normal deep reflex. The reflex may vary from time to time in healthy individuals, it may sometimes be very brisk but then it is uniform in degree. Differences in one side or the other, or differences in liveliness in the same extremity, e.g., between the knee and the ankle jerks, should make one suspicious of organic involvement of the pyramidal system. It is important to recall that for a time after sudden paralysis due to corticospinal neuron involvement, there is at first a loss of reflexes, supposedly initiated by the so-called shock (cerebral or spinal).

- 2 *The superficial* (also called cutaneous) *reflexes*, e.g., abdominal or cremasteric, *are usually diminished or lost* on the side of the paralysis. There are many ingenious theories to explain this fact, but none

of them has been proved, besides, in many cases the superficial reflexes are not lost at all, and again, in other instances, they are lost only temporarily.

There may be abnormal associated movements which can be observed only when the spasticity is quite marked. Their interpretation is not easy and not always satisfactory.

Atrophy, in the real meaning of the word, does not develop in the involved muscles. There may be some atrophy from nonuse, and after a duration of years there may be slight diminution of response to electric stimuli but never leading to the reaction of degeneration.

### THE BABINSKI SIGN

It is apparent that so far we have not encountered a sign which could be used alone as an absolute indicator of organic involvement of the pyramidal tract. There was no known single objective sign definitely proving the involvement of the corticospinal fibers until the advent of Babinski's fundamental finding of the 'upgoing great toe' when the sole of the foot is scratched or stroked. This sign became one of the most important in clinical neurology. Babinski's sign is always pathognomonic of some involvement of the pyramidal pathway, except in very rare instances when none of the extensors of the great toes are involved and all its short flexors are paralyzed by spinomuscular (also called lower motor, peripheral, nucleomuscular) neuron involvement, and in the case of infants up to the age of walking. Until this time the presence of a Babinski sign is suggestive of nonmyelination of the corticospinal fibers. It might be mentioned here that infants may, and frequently do, suffer from lesions of the pyramidal tract, and that problems of differential diagnostic importance may be encountered in them.

In passing, we may mention that there are short-lived Babinski signs, e.g., during general anesthesia, poisoning with barbiturates or with the belladonna group—especially scopolamine—during insulin and uremic coma, during Cheyne-Stokes' respiration, in normal sleep (?) following convulsive seizures—idiopathic or otherwise—and in the wake of artificially induced convulsion. In these cases it is supposed that anoxia or some other transient interference with the pyramidal function produces temporary inactivity.

**Technic of Elicitation**—No matter how objective a certain sign may be it cannot be evaluated as easily as, for example, a chemical reaction as long as it must depend on some activity on the part of the physician. This is one of the reasons why time and experience are required before we can confidently state whether or not a certain reflex is

elicited. There is no problem to solve when any of the pathologic reflexes is fully developed. Lack of evaluation of the minor signs and improper technic are causes for misinterpreting a reflex.

It is generally accepted now that the responses to the Chaddock, Oppenheim and Gordon techniques are nothing more than the Babinski sign elicited from different parts of the wide receptive field for the "upgoing toe." However, exact knowledge of the technic of their elicitation is not without benefit to our diagnostic skill. The soles of some patients are so tender or are injured in such a way, as to prevent the examiner from touching them. In such cases the other techniques might be very useful. Besides, if we elicit dorsiflexion of the big toe with more than one technic, we are more fully convinced that we are dealing with a lesion of the pyramidal tract.

In trying to explain the techniques of elicitation of the pathologic reflexes which are generally used at the present time, I shall deviate somewhat from the usual presentation and submit the techniques as they have proved most dependable in my experience. In every instance I shall give the technic or techniques which, according to my investigation, have been most satisfactory in eliciting responses, even in their slightest manifestations.

The time has arrived for establishing a standard reflex technic. This would assist physicians everywhere to understand a certain technic and to evaluate and interpret the responses more uniformly. There is lack of uniformity in the clinical examination, as well as in the important animal experimentations. I know only too well that absolute uniformity cannot be achieved, but this should not deter us from attempting to reach such a goal.

*Plantar Responses*—I prefer a simple pin for eliciting the plantar responses, although a wooden applicator or match may also be used. Chaddock recommended a moderately pointed nail file. It is advisable to use the same type of instrument and to become accustomed to its use. Many contraptions have been recommended, and, in an attempt to standardize the method, "special stimulators" have been designed, but none of them has been generally accepted.

The *recumbent position* of the patient is best for eliciting the plantar responses. The patient is asked to relax if there is no unsurmountable spasticity or he is not unconscious. In the great majority of cases, withdrawal of the limb can be expected, it is, therefore, advisable for the examiner to grasp the leg of the patient just above the instep. This will guard against excessive withdrawal and will keep the foot in a position so that the movements of the toes may be observed to best advantage. The elicitation of responses is begun slowly from the

els forward, at first using slight stimulation, and holding the pin most parallel with the sole of the foot. In this manner unsightly scratch marks on the sole of the foot are eliminated. If there is no response to mild stimuli, or if the sole is calloused, stronger stimulus needed. In such cases the point of the pin becomes very handy. If slight stimulus does not suffice it is strengthened gradually until a flex movement is noticeable. Ankylosis in the metatarsophalangeal joint of the big toe and extreme spasticity of the muscles of the foot prevent any movement of the big toe. Athetoid movements may greatly interfere with correct interpretation of the direction of the toes.



Fig. 15—The optimum location and the direction of stimulus for the elicitation of the Babinski sign

The manifestation of the physiologic plantar reflex is the plantar flexion of all of the toes in the metatarsophalangeal joints. This flexion is quick and almost always accompanied by flexion movements of the ankle, knee and hip joints, as well as by contraction of the calf muscles and of the tensor fasciae femoris muscle. The normal plantar response is best elicited from the mesial border of the sole. On the other hand the optimum location for the elicitation of the Babinski sign is from the lateral border of the sole (Fig. 15). The normal response and the Babinski sign if well developed, may also be obtained by stimulation of any part of the sole.

The elicitation is begun with a mild stimulus, striking from the heel upward to, but not including, the ball of the foot, describing an inward curve just before reaching the base of the toes. If there is no response after repeated strokes, applying more force to each consecutive stroke, only then may we state that the Babinski sign is absent. Any differences between the two sides should be noted, as well as differences between the successive responses on one side, that is, the "upgoing toe" may alternate with the plantar flexion. In the early stages of pyramidal tract involvement, these minor alterations may be the first signs of beginning loss of function of the tract. When the Babinski sign is fully developed, it manifests itself in slow and forceful dorsiflexion of the big toe. Great care must be exercised not to interpret protective movements of the toes as reflex movements—this may not always be an easy task.

Frequently, we may also observe a spreading (fanning) of the other toes simultaneously with the "upgoing toe." The direction of these outer toes is generally horizontal, but they may turn downward or upward. At times all five toes dorsiflex without spreading. Very frequently, in addition to the toe movements, there is dorsiflexion in the ankle joint and flexion in the knee and hip joints. Contraction of the calf muscles and of the tensor fasciae latae can be observed most frequently, if we are looking for it. These widespread movements constitute the reflex flexion-defense withdrawal of the limb. According to the most widely accepted conception at the present time, the dorsiflexion of the big toe (still referred to as "extension" in general usage and in many textbooks) is but a component part of this defense reflex. Whether or not this is true, the fact remains that the most important and only definite pathognomonic movement is the dorsiflexion of the big toe. Flexion movements in the other joints, as already mentioned, occur also in the absence of pyramidal involvement.

It is of importance to know that in definite lesions of the pyramidal pathways we may encounter plantar flexion of the toes, including the big toe, by correctly executing the Babinski maneuver. Many neurologists consider this phenomenon as a sign of very severe and irreparable damage to the pyramidal tract. My own experiences with gunshot and stab wounds of the spinal cord during World War I are in accord with this observation. If the patient survives for a few months this plantar flexion usually changes to dorsiflexion.

**Chaddock's Technic**—Among the confirmatory methods, Chaddock's technic is the most sensitive. It consists in stroking the skin around the external malleolus in a circular direction, as depicted in Fig. 16. This single stimulation includes two separate areas originally recom-

nended by Chaddock as being the most sensitive for the elicitation of the reflex. The technic is to begin with a slight stimulation, stead

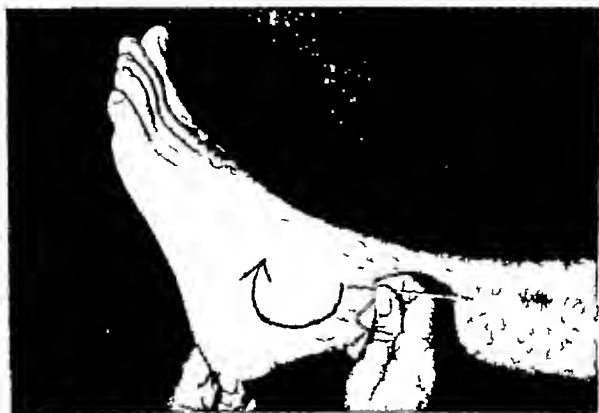


Fig 16—Chaddock's technic for elicitation of the pathologic plantar response.



Fig 17—Oppenheim's technic

ily increasing it until the pressure reaches its maximum at the end and maintaining this pressure for a few seconds before removing the

stimulator. If there is no response, the force of the stimulation is increased from the beginning of its application to the end. This stimulated area is much less sensitive than the sole, therefore, the stimulus used in the Chaddock technic, besides being an indicator of pyramidal involvement if the big toe dorsiflexes, also decreases the voluntary withdrawal movements of the limb to a great degree. It is well to repeat the maneuver several times before declaring that there is no response. It may be that the "summation" of stimuli explains that fact that occasionally, when the first applications do not evoke a response, the consecutive ones will, especially if the pressure is increased. These observations are valid concerning the other technics also.



Fig. 18—The technic of Gordon

**Oppenheim's Technic.**—The next technic in frequency to indicate pyramidal fiber involvement is the technic of Oppenheim (Fig. 17). Theoretically, in this technic the leg is divided into three equal sections and stimulation is begun at the top of the middle third. The thumb is pressed firmly on the inner border of the tibia, with a downward stroke, until reflex toe movements are noted. This usually occurs when the upper limit of the lower third is reached. At times it is necessary to strike down to the internal malleolus with increasing force before the reflex can be obtained. Only after repeating these manipulations several times, without a resulting dorsiflexion of the big toe, should we conclude that the Oppenheim method has failed.

**Gordon's Technic.**—We are still using the Gordon technic routinely (Fig. 18) but this may soon be discarded because this reflex is never present when those previously mentioned are absent. While we adhere to the technic for its elicitation, it is best to follow Gordon's original recommendation, namely, to stand at the outer side of the leg, rotate the foot slightly externally, press the fingers deeply upon the middle or lower portion of the calf muscles, simultaneously pressing with the thumb on the opposite portion of the same muscles. As in all previous technics, we consider the reflex sign to be present if the great toe dorsiflexes.

When extreme sensitivity of the patient interferes with the application of any of the mentioned technics I find it very helpful to divert the patient's attention from the manipulation by having him strain enough or breathe deeply.

Many other technics have been described. All of them have had a fair trial, but they have either not given positive results in a large enough number of cases or there were no benefits to be derived from their use so that they have become obsolete.

#### THE ROSSOLIMO SIGN

Not until Rossolimo described his sign did we have a really new contribution to the subject. This is not a modification of the technic of Babinski, but is an entirely different method of showing corticospinal tract involvement in the lower extremities. With this technic the tendons of the toes are primarily stimulated—shortened or lengthened. Thus the stimulus is proprioceptive in contradistinction to the Babinski method where the stimulus is exteroceptive. In addition, as will be explained, the responses to the stimuli are different. The Rossolimo sign can be elicited by (*a*) short, quick upward taps to the plantar surface of the toes, or (*b*) hitting the ball of the foot with a percussion hammer or (*c*) hitting the tips of the toes perpendicularly (Fig. 19) with a sudden downward flap of the extended and stiffly held fingers quickly withdrawing the hand so as to enable the examiner to observe the reflex movements of the toes. There will be no movement of the toes in healthy persons, or in extremely rare instances a slight dorsiflexion may ensue. However, in the presence of pyramidal tract lesions there is plantar flexion in the toe which has been struck or in the other toes also. At times only the outer toes flex in plantar direction or only the big toe flexes in this direction and at other times all the toes execute the same movement. All of these movements may be accompanied by slight abduction of the toes. A negative response should not be accepted until the above stimuli have



been repeated, with increasing force if necessary, using the different stimuli described above. The Rossolimo sign thus executed is a good



Fig. 19—One of the variations of the techniques for eliciting the Rossolimo sign—hitting the tips of the toes perpendicularly

test for proving pyramidal tract involvement. This sign may be present in many cases of early multiple sclerosis when the aforementioned signs are not, or are only equivocal.

#### THE HOFFMANN SIGN (INCLUDING TROMNER'S TECHNIC)

Thus far we have described only those signs which are definite indicators of pyramidal tract involvement. Before describing another reflex, which seems to be an even more sensitive test for detecting lesions of this tract, we shall mention the Hoffmann sign and clonus which may be obtained at times when there is no demonstrable lesion of the pyramidal tract. In a small percentage of men, when the Hoffmann or the Tromner technic is applied, we have noticed flexion of the digits in those exhibiting general hyperreflexia. This was found to be present in approximately 2 per cent of apparently normal college students. I have found this reflex in about the same percentage of otherwise healthy appearing men (ages 17 to 38) during induction for military service, and in a much greater percentage of patients suffering from idiopathic epilepsy (use of barbiturates?). In all these cases the responses were bilateral and equal. Naturally, slight symmetrical birth injuries or unobserved diseases of the central ner-

ous system could not be excluded in all of the cases. We should also consider this sign as a possible early indication of disease which has as yet no other manifestations. It would be a rare finding, however, if in any of these instances the Hoffmann sign were equal on both sides.

I have never missed finding the bilateral appearance of the Hoffmann sign after electrically induced convulsions. It lasts only a few minutes during the stage of flaccidity of the muscles. I emphasize this fact because many neurologists still believe that the Hoffmann sign



Fig. 20.—The technic for elicitation of the Hoffmann sign. Note the dorsiflexion of the hand.

is nothing but an indication of spasticity of the muscles. It is not a sign of spasticity, although spastic muscles greatly enhance the flexion movements of the fingers. I have had the opportunity to demonstrate the presence of this reflex in cases of unilateral flaccid paralysis as a definite sign of corticospinal neuron involvement.

**Technic.**—For obtaining the best results with this method, first dorsiflex the hand at the wrist joint (the dorsiflexion acts as reinforcement), then firmly grasp the middle phalanx of the semiflexed middle finger with two fingers (Fig. 20). Stabilizing the hand in this manner

been repeated, with increasing force if necessary, using the different stimuli described above. The Rossolimo sign thus executed is a good



Fig. 19—One of the variations of the technique for eliciting the Rossolimo sign—hitting the tips of the toes perpendicularly

test for proving pyramidal tract involvement. This sign may be present in many cases of early multiple sclerosis when the aforementioned signs are not, or are only equivocal.

#### THE HOFFMANN SIGN (INCLUDING TROMNER'S TECHNIC)

Thus far we have described only those signs which are definite indicators of pyramidal tract involvement. Before describing another reflex, which seems to be an even more sensitive test for detecting lesions of this tract, we shall mention the Hoffmann sign and clonus, which may be obtained at times when there is no demonstrable lesion of the pyramidal tract. In a small percentage of men, when the Hoffmann or the Tromner technic is applied, we have noticed flexion of all the digits in those exhibiting general hyperreflexia. This was found to be present in approximately 2 per cent of apparently normal college students. I have found this reflex in about the same percentage of otherwise healthy appearing men (ages 17 to 38) during induction for military service, and in a much greater percentage of patients suffering from idiopathic epilepsy (use of barbiturates<sup>2</sup>). In all of these cases the responses were bilateral and equal. Naturally, slight symmetrical birth injuries or unobserved diseases of the central nerv-

ous system could not be excluded in all of the cases. We should also consider this sign as a possible early indication of disease which has as yet no other manifestations. It would be a rare finding however if in any of these instances the Hoffmann sign were equal on both sides.

I have never missed finding the bilateral appearance of the Hoffmann sign after electrically induced convulsions. It lasts only a few minutes during the stage of flaccidity of the muscles. I emphasize this fact because many neurologists still believe that the Hoffmann sign



Fig. 20.—The technic for elicitation of the Hoffmann sign. Note the dorsiflexion of the hand.

is nothing but an indication of spasticity of the muscles. It is not a sign of spasticity, although spastic muscles greatly enhance the flexion movements of the fingers. I have had the opportunity to demonstrate the presence of this reflex in cases of unilateral flaccid paralysis as a definite sign of corticospinal neuron involvement.

**Technic.**—For obtaining the best results with this method, first dorsiflex the hand at the wrist joint (the dorsiflexion acts as reinforcement) then firmly grasp the middle phalanx of the semiflexed middle finger with two fingers (Fig. 20). Stabilizing the hand in this manner

proves to be of great benefit in observing the reflex movements of the other fingers. Next grasp the end phalanx of the patient's middle finger between the thumb and the index finger of the free hand and suddenly bend and release it (this is a modified technic of Hoffmann's, who never reported his reflex), or snap the palmar tip of the middle finger with a quick, firm upward flick (one of Tromner's many recommendations). The fully developed response manifests itself in an immediate flexion of the thumb and of all of the other fingers. *Many investigators, including myself, do not consider the Hoffmann reflex to be present if the thumb does not flex.*

To avoid confusion and to honor the man who first used it, we generally speak of this phenomenon as Hoffmann's sign. I have mentioned this sign as one which might be present only bilaterally in supposedly healthy individuals. Naturally, it might also be present bilaterally in a case of bilateral pyramidal tract involvement anywhere above the fourth cervical segment, but in this latter instance other concomitant signs of pyramidal tract disease will lead to a correct diagnosis.

If the Hoffmann sign is elicited properly and is obtained unilaterally only, it becomes the most sensitive sign of pyramidal tract involvement of the upper extremity. Several other reflexes are recommended for the purpose of diagnosing pyramidal involvement of the upper limb, but in my experience none—not even the Mayer sign—ever approaches the value of the Hoffmann sign. In many cases, in applying the Hoffmann technic, especially when there is spasticity of the muscles of the upper extremity, the whole arm jerks with simultaneous abduction of the shoulder and flexion in the elbow joints. I would like to mention a finding of mine which I have not seen recorded elsewhere, namely, that occasionally repeated and proper stimulation with the Hoffmann technic does not lead to flexion of the digits until the Tromner method has been applied immediately preceding the Hoffmann technic.

The hand area has a widespread representation in the motor cortex. The Hoffmann sign is diagnostic of a lesion in this cortical area and may point to the exact location, thus saving lives, e.g., by early removal of a neoplasm pressing upon the hand area. In such cases the Hoffmann sign is present without the Babinski sign.

#### CLONUS AND SUPRAPATELLAR REFLEX

To elicit the *ankle clonus* we bend the lower extremity in the hip and knee joints, and supporting the leg with one hand we suddenly dorsiflex the foot with the other hand, using moderate force. After reaching the maximum dorsiflexion the upward pressure is released

and thereafter moderate pressure is continuously sustained. If alternating plantar flexion and dorsal flexion of the foot ensue, we may state that ankle clonus is present. This clonus may be sustained or it may be of short duration. Many times when we are unsuccessful in obtaining a clonus in the manner described above, we may obtain it by holding the foot in a maximally dorsiflexed position and hitting the Achilles tendon with a brisk blow of the reflex hammer.

The *patellar clonus* is best elicited with the leg extended. The upper border of the patella is pressed suddenly downward with the thumb and forefinger, releasing the force of the downward pressure by holding the fingers steadily with moderate pressure. If alternating upward and downward movements of the patella follow, this indicates the patellar clonus. Occasionally, when this technic fails, I often obtain patellar clonus when I hit my forefinger, which is bent around the upper border of the patella, in a downward direction.

The *suprapatellar reflex*, which consists in an upward movement of the patella when the forefinger is hit in exactly the same manner as is described for the elicitation of the patellar clonus, is less frequently elicited than the regular patellar reflex. When bilaterally and equally present the suprapatellar reflex shows only general "reflex hyperirritability," but when present unilaterally it signifies a pyramidal lesion anywhere above the second lumbar segment.

The *wrist clonus* is found only in pronounced spasticity of the upper extremity. It is elicited by sudden dorsal flexion of the hand but clonus is not present until alternating upward and downward movements are seen.

#### THE GONDA SIGN

There are many controversial and unsolved problems in the interpretation and correlation of the findings in pyramidal tract involvement, e.g., it has not yet been definitely decided whether a certain part of the pyramidal system is involved when the Rossolimo sign is elicited and another when the Babinski sign is present. Some neurophysiologists have reported the finding of separate areas governing the "upgoing toe" part and the "fanning" component of the Babinski sign. It seems to me that as far as the Babinski and its related signs are concerned, 'organic' destruction or some temporary "functional" suspension of a certain percentage of the pyramidal tract fibers is necessary before pathologic signs can be elicited. This assumption might be of some importance for clinical and experimental purposes. If this conception could be considered as valid, then we could state that the Chaddock technic yields positive results with approximately the same extent of corticospinal involvement as the Babinski technic.

but the lesion must be more extensive for the Oppenheim or Gordon technic to result in the phenomenon of the "upgoing toe"



Fig 21—*Upper*, The technic and manifestations of the Gonda sign. Note the firm grip and twisting of the fourth toe. *Lower*, Occasionally only the flexing of all the outer toes results in dorsiflexion of the big toe.

**Technic**—In 1941, I described a sign and called it "tendon stretch reflex." Clinically and experimentally (in primates), this sign proved to be a more sensitive indicator of pyramidal tract involvement for the lower extremity than any of the previously described methods. The





ception I would not accept as confirmation of this statement the fact that prior to Tromner another neurologist stated that the tendons are only "conveyors" of the reflex mechanism. It was stated recently that the tendons are merely "dead tissue." They may be dead, but they have a nerve supply with special terminal fibers called the "organs of Golgi." It is easily conceivable that stimulation of these end organs in the tendons, even without any stretch of the muscles, might excite enough afferent impulses on the reflex arc to elicit a reflex.

**Advantages of Method**—Much study and experimentation will have to be done before this complicated problem will be solved scientifically. Meanwhile I should like to mention that this new technic, for the first time, led to a definite dorsiflexion of the big toe in lower primates (*Macaca mulatta*). In higher primates (chimpanzee), with experimentally produced pyramidal tract lesions, it is also a more sensitive sign than those used previously. It may be of great practical importance that in those diseases of the central nervous system in which other tracts besides the pyramidal system are also involved—e.g., amyotrophic lateral sclerosis, Friedreich's ataxia—and when the Babinski, its confirmatory signs and the Rossolimo sign may not be elicited, my method may be the only one which will definitely prove the presence of pyramidal tract lesions. Besides these advantages and those mentioned previously, it may contribute to the solution of the controversial question as to what constitutes the toe response in newborn infants and children up to the age when it changes to normal plantar reflex. And last, but not least, because this sign is never present in individuals not suffering from diseases of the pyramidal pathway, it will help more than any other method in making a differential diagnosis between organic lesions of the nervous system and symptoms caused by certain types of psychoneuroses or war neuroses. In these latter cases the deep reflexes may be exceedingly lively and paralyzes may appear which closely resemble "organic" palsies.

#### BIBLIOGRAPHY

- 1 Babinski, J. Sur le réflexe cutané plantaire dans certaines affections organiques du système nerveux central. *Compt. rend. Soc. de biol.*, 3 207, 1896.
- 2 Babinski, J. Du phénomène des orteils et de sa valeur sémiologique. *Semaine med.*, 18 321-322, 1898.
- 3 Babinski, J. De l'abduction des orteils. *Rev. neurol.*, 11 728, 1903.
- 4 Chaddock, C. G. A Preliminary Communication Concerning a New Diagnostic Nervous Sign. *Interstate M. J.*, 18 742-746, 1911.
- 5 Curschmann, H. Ueber die diagnostische Bedeutung des Babinskischen Phänomens in präcuraeischen Zustand. *München med. Wchnschr.*, 39 2054-2057, 1911. (This paper gives the first description of the Hoffmann sign.)

- 6 Echols, D H The Hoffmann Sign Its Incidence in University Students  
J Nerv & Ment Dis., 84 427-431 1936.
- 7 Gonda, V E. Treatment of Mental Disorders with Electrically Induced  
Convulsions Dis Nerv System 2 84-92 1941
- 8 Gonda V E A New Tendon Stretch Reflex Its Significance in Lesions of  
the Pyramidal Tract Arch Neurol & Psychiat., 48 531-536, 1947
- 9 Gonda, V E. Experimental Lesions of the Pyramidal Tracts in Primates,  
Accompanied by a New Reflex J Neuropath & Exper Neurol., 1 344-  
347 1942
- 10 Gordon, A Paradoxie Flexor Reflex Its Diagnostic Value Am Med., 8  
971 1904
- 11 Oppenheim H.. Zur Pathologie der Hautreflexe an den unteren Extremitäten.  
Monatsch f Psychiat. u Neurol., 12 518-530, 1902
- 12 Rossolimo G J Der Zehenreflex (ein speziell pathologischer Sehnenreflex)  
Neurol Zentralbl., 27 452-455 1908
- 13 Trömner E. Pathognostischer Fingerreflex, Fingerbeugephänomen Neurol  
Zentralbl., 31 603 1912
- 14 Trömner E. Ueber Sehnen resp Muskelreflexe. Ber klin Wehnschr., 50  
1712 1913

# SUBDURAL HEMATOMA

ERIC OLDBERG, M D \*

In this clinic I wish to describe and illustrate an entity which, despite its comparative frequency, still remains on occasion a neglected or unsuspected lesion for the general practitioner, and a difficultly diagnosed one for the neurologist or neurosurgical specialist. It is always on our "must" program for teaching medical students, and it fortunately falls into that category of cases, in our sometimes somber field, in which we may expect a large majority of complete and permanent cures if we can but be alert to and capable of recognizing the condition.

A subdural hematoma, as its name implies, is a hematoma which exists beneath the dura—between that membrane and the arachnoid. It is therefore separated from the brain proper by the pia, the arachnoid and the intervening space between these layers which contains the cerebrospinal fluid, and from the potential space between the dura and the bone of the skull by the dura mater. In this respect, its location is different from the position occupied by a meningeal arterial hemorrhage, an infinitely less common lesion, in that the latter almost invariably lies either outside the dura, in the space between that structure and the bone, or between the layers of the dura itself.

## PATHOLOGIC FACTORS

For years subdural hematomas were confused pathologically with what Virchow had described as *pachymeningitis hemorrhagica interna*—a condition of supposed spontaneous subdural bleeding occurring in alcoholics, demented patients, patients with conditions causing cerebral atrophy such as general paresis, and so on. Head trauma was regarded as a possible auxiliary factor, but it was Virchow's idea that the meningeal change, or meningitis, was primary, and that the bleeding was resultant and secondary. Since the time of Virchow this opinion has altered, so that it is now even doubtful that any such entity as described by him ever exists, at least in the manner he imagined.

Instead, a subdural clot is now generally accepted as having its

---

From the Department of Neurology and Neurological Surgery, University of Illinois College of Medicine, and the Illinois Neuropsychiatric Institute, Chicago.

\* Professor of Neurology and Neurological Surgery and Head of the Department, University of Illinois College of Medicine.

origin in trauma, the meningeal changes being merely reactive phenomena. Those few exceptions which are unassociated with trauma are caused by vessel erosion from such a rarity, perhaps, as miliary meningeal carcinomatosis, but here again, the bleeding is primary as far as the formation of the condition is concerned.

*The method of formation* of subdural hematomas is interesting. They are usually confined to the convexities of the cerebrum, and most commentators agree that the source of the hemorrhage is from the fragile veins in the region of the sagittal sinus. Every neurological surgeon knows from experience that the tensile strength of the venous vessel walls in this region is so slight that the amount of direct trauma such as that from forceps or a cotton pledget, necessary to rupture them is almost infinitesimal. They are therefore situated and constructed in such a way as to be easily stretched and torn by outside trauma to the head, for on the one hand they are attached to the comparatively mobile brain which may be suddenly jolted out of position, while on the other they are connected to the relatively rigid sagittal sinus. That these lesions are almost unknown over the cerebellum is therefore explainable by the fact that no veins join its cortex to the median or straight sinus.

**Trauma**—This brings up the question of the amount of trauma necessary to initiate this pathological condition. It is a seemingly paradoxical fact that most of the cases of subdural hematoma that one sees clinically have resulted from rather trivial injuries. On the other hand, out of the plethora of cases of severe cerebral damage with skull fracture which constantly pass through our hospitals it is the exceptional patient who subsequently develops a subdural hematoma. Various explanations have been offered for this phenomenon, involving such things as individual variations in the tendency to bleed, in the constituents of the blood, and so forth. To me, the logical explanation seems to lie in two factors which have been elaborated by Putnam: first, that in severe injuries there is so much immediate edema of the brain that bleeding does not progress very far before it is stopped by pressure, and second and conversely, that when no such edema and pressure obtain, the brain sags away from the skull and dura when the patient is in an upright position, and thereby enhances the enlargement of the clot.

Whatever the cause we may say that it is not only possible but usual for comparatively minor injuries to the skull to be the cause of subdural hematoma. That they should occur more frequently in older individuals is readily understandable upon the basis of the increased fragility of the veins with age. This does not preclude their occur-

rence even in infants, however, upon whom reports have been made by Peet and Kahn, Naffziger, and others

**Process of Formation**—When trauma to the head occurs sufficient to rupture one or more of the veins traversing the subdural space on their way from the cortex to the sagittal sinus, the first thing which takes place is the extravasation of blood into the subdural space, and the formation thereby of a thin but extensive clot. This clot will almost always cover the whole of one hemisphere, and in some instances both hemispheres, if veins on both sides are torn. In a small proportion of such cases, the clot then becomes completely organized without liquefying, and the blood cells contained in it are destroyed in the process. In another small proportion, a minimal amount of blood becomes very largely mixed with cerebrospinal fluid escaping from a rent in the arachnoid, and such collections of fluid, becoming encysted in fibrin and mis-called subdural hygromas, may occasionally remain in status quo for years. This fact has been pointed out and well substantiated by Munro and Merritt.

In the great majority of cases of subdural bleeding, however, the resultant clot undergoes a series of interesting pathological steps. First, as in all clots, it becomes encased in a layer of fibrin which precipitates from it and surrounds it, the center becoming liquid through disintegration. The contiguous dura, which forms the parietal boundary, then begins proliferating fibroblasts, a layer of which eventually sweeps around the entire clot, invading the fibrin. This layer of fibroblasts is thick and finally becomes vascularized at its attachment to its dural source. The distant layer springing from the same source, and covering the visceral boundary of the hemorrhage, remains thin and avascular, however, for it is contiguous to the arachnoid which is devoid of blood supply.

The entire original clot, then, becomes a closed sac composed of semipermeable, dialyzing membrane, containing within itself a liquefied protein substance which is constantly breaking down through disintegration and producing a material of great osmotic differential to cerebrospinal fluid, and separated from that liquid only by the thin arachnoid and a thin fibroblastic layer. The result, of course, is that cerebrospinal fluid dialyzes through until the osmotic pressure of the hematoma fluid and the spinal fluid has equalized.

It has been estimated that this process continues for about three months, and the gradual growth by such a method of this "tumor" would explain the slow progressive symptoms of the disease. Certain it is that almost every hematoma one operates upon is startlingly enormous. At least one hemisphere is usually completely covered, and

mass thicknesses of two inches are not uncommon. There is a disparity in report as to the percentage of bilaterality, but I would estimate it to be 20 to 25 per cent.

**Surgical Pathology**—When the dura over such a lesion first comes into view it has a peculiar bluish hue, which is apparent through even so small an opening as a burr hole. Upon opening the dura, a greenish membrane is encountered which is more or less attached to it, of course by organization of fibrin. The greenness of the membrane has often been remarked upon, and has been attributed to transformation of blood into bile pigment by the reticulo-endothelial cells in the dura. When this green membrane is perforated, the liquid and major portion of the hematoma gushes out by the ounce, the color varying all the way from moderate xanthochromia to almost ink black. This discloses the greenish, thin, opalescent membrane of the visceral portion of the sac lying loosely and unattached upon the arachnoid. Removal of it reveals the normal, intact arachnoid.

#### CLINICAL FEATURES

How does all the foregoing discussion influence the clinical features associated with subdural hematoma? First, there will usually be a history of *injury to the head* more often than not of insufficient severity to produce unconsciousness. Sometimes this history of trauma cannot be obtained, either because the patient has forgotten it and his relatives have not known it, or because the patient has become mentally aberrant. I, myself, have seen two successive patients from whom no traumatic history was obtained, who, when mentally reoriented following operation, recollected having bumped the tops of their heads against automobile doorways when mounting the running board, and I have seen another who did the same against the door at the head of his basement steps.

Following the injury there will be a *latent period*, usually lasting from two or three weeks to several months. During this time the patient may feel perfectly well, or, as is more often the case, he will have no complaint other than that of a dull and rather persistent headache. Then symptoms definitely attributable to direct cerebral embarrassment begin to appear. These may present themselves as focal and purely neurologic findings, but in my experience the commonest initial cerebral manifestation is *mental aberration*—aberration of no special variety but taking the form of a new-found silliness, forgetfulness and untidiness. This experience is borne out by the fact that routine autopsies upon patients committed to hospitals for the insane always

show their quota of unsuspected subdural hematomas, the figures sometimes running as high as those reported by Allen, Daly and Moore in 1935, showing 245 cases in 3100 consecutive autopsies upon psychotic persons

Other than or in addition to psychosis, or at least deterioration, the neurologic symptoms may be legion, as would be expected of a lesion covering such an enormous territory as an entire hemisphere, and sometimes both hemispheres. These symptoms may be not only more or less cortical, as would be evidenced by such conditions as aphasia or hemiparesis, but they may be bizarre—homolateral paralysis sometimes occurring because of pressure of the opposite cerebral peduncle against the edge of the incisura tentorii, or homolateral homonymous hemianopsia being produced by impingement of the lateral geniculate body upon the same structure. In general, however, the definite neurologic symptoms will be accompanied by clinical signs which, when integrated, will prove logical and will provide clues indicating the underlying pathologic condition.

**Clinical Signs**—In the description of the clinical signs of a condition which reveals itself in such a multiplicity of ways as does subdural hematoma, it is difficult to decide upon a proper order of presentation. First, of course, comes objective evidence of *mental aberration*. Perhaps next most common is the evidence of *long-standing increased intracranial pressure*. This can be determined in the usual way by the examination of the optic fundi and, in addition, can be corroborated by lumbar puncture. Usually one abjures lumbar puncture in the presence of choked disk, but in suspected hematoma it is valuable because the discovery of xanthochromic fluid greatly aids in the diagnosis, though it is not necessarily present, and because a normal fluid pressure in association with intermittent stupor, headache, and so on, is also significant owing to the frequency with which it occurs—usually in old clots to which the brain has more or less accommodated. *X-ray examination of the skull* is also important for, if the pineal gland should happen to be visible, it has been said on good authority to be pushed further out of position by hematomas than by any other single type of lesion. In addition to these general signs, there may be various focal ones, the most common in my experience, being aphasia and mild signs of hemiparesis such as central facial weakness and characteristic reflex changes.

#### CASE REPORTS

The following cases illustrate the condition and manifest certain typical variations of it. The first example is an ordinary one with a

successful conclusion, and I would say that it represents fairly well 75 per cent of the cases encountered

**CASE I**—This patient was a 40 year old dock foreman, whom I first saw some six weeks after the date of his injury. The injury had occurred when the patient stepped upon a slack cable, which was suddenly tautened by a donkey engine, tossing the patient some 10 feet in the air and somersaulting him to the wooden flooring of the dock. The patient's head was severely bumped, but he was not knocked actually unconscious and was only dazed for a few minutes. He was taken to the hospital by the company physician, where x-ray plates of the skull were taken which revealed no abnormality and a midline pineal body. The patient remained at home for a week during most of which time he was up and about the house and he then returned to work and worked steadily for three weeks, although during this time he complained of ceaseless headache, which gradually became more severe as time went by. Finally it became so severe that the patient was again advised to rest at his home and this he did for a week, being out of bed a good deal of the time but the increase in his discomfort became so great that he was rehospitalized and had been so for one week at the time I first saw him.

At this time the patient was normal neurologically and skull plates had not been repeated. The optic fundi showed no sign of pressure, but a lumbar puncture yielded clear and colorless fluid under the moderately elevated pressure of 275 mm. of water.

Three days later a second puncture showed a pressure of 350 mm., and in three to four more days the patient developed bilateral early papilledema. He also became somewhat aphasic and euphoric, developed a slight right lower facial weakness and x-ray plates of the skull showed a 2 cm. shift of the pineal body toward the right.

A left parietal bur hole was accordingly made, and the dura opened and a large subdural hematoma identified. A moderate-sized centrally placed osteoplastic flap was therefore reflected, and it was obvious that the hematoma covered the entire convexity of the hemisphere. It was about 3 cm. in thickness and when evacuated the yellowish cortex of the brain fell away from the inner table of the skull quite markedly. The patient was given 1000 cc. of half-normal saline solution intravenously and placed in bed with the foot of the bed elevated and the patient lying on his left side.

Within a week the optic fundi, aphasia, mental change and facial weakness had all disappeared. The spine was repunctured on the eighth postoperative day and the pressure seen to be normal. The patient was up and about on the ward several days before his discharge, two weeks from the day of his operation. Within three months he was back at work, and he continued at this occupation for ten years until he finally died of cardiorenal disease.



Not all patients attain the happy result of Case I, however I would say that one of the most dangerous and difficult problems with which the neurosurgeon has to deal is the situation in which he is forced by circumstances to take immediate action in a case in which active bleeding may still be in progress. Case II illustrates why I have taken the stand that under all circumstances, even in the face of our usual dictum against moving head-injury patients, I must operate in such situations in my own hospital with my own staff. The time element alone, if spent waiting for a willing but unfamiliar nurse to respond to one's needs and wishes, may swing the balance.

CASE II—This patient, a 52 year old hospital superintendent, was seen ten days after his injury. The injury had occurred in an automobile collision in which the patient, who was driving his car, collided with another and bumped his head against the windshield, producing about one-half hour of unconsciousness. On regaining consciousness the patient drove his own car to the hospital of which he was superintendent and received first-aid therapy, had x-ray plates of the skull taken, which were negative and in which the pineal body was not calcified, and rested a few hours. On the following day he returned to work and worked for several days, despite an increasingly severe, generalized headache. This finally grew to be of sufficient proportions to produce vomiting on a couple of occasions and the patient, therefore, reentered the hospital, where he had been for three days prior to my visit to him on the tenth day after his injury.

On this visit the patient was sitting on the side of his bed with a table drawn in front of him and was signing the pay checks of the various hospital employees. He was alert mentally but complained of terrific headache. There was bilateral early papilledema but otherwise the patient was neurologically negative. He had been a known hypertensive for a number of years, and his blood pressure was 200/110.

A spinal puncture was performed which yielded xanthochromic fluid under a manometric pressure of 500 mm of water. Within forty-eight hours the patient's headache had increased to an almost unbearable point, and he was becoming stuporous. This progressed so rapidly that by the time operative arrangements were completed and I could arrive at the hospital with instruments, which was about two hours, the patient was in coma. A burr hole was placed over both parietal areas, about 3 cm from the midline, and a bilateral subdural hematoma was disclosed.

There was a thick, red clot and, in addition, continuous bleeding which it seemed impossible to stop. It finally did cease, however, after the patient's blood pressure had dropped, and a small piece of muscle was implanted in the hope that this would help prevent further bleeding. Within eighteen hours, however, the patient, who had not re-

gained consciousness, went into extremely deep coma, his blood pressure rose to 240/140, and his temperature began to rise, having reached about a degree above normal at the time I was called. He was accordingly transferred to my hospital by ambulance immediately, while the operating room was made ready. I reentered the old operative incision about twenty-four hours from the time of the previous operation, and on opening up the field was again met by profuse and uncontrollable bleeding. The patient had a convulsion on the table, his blood pressure rose to unmeasurable heights, and finally, after removing bone with rongeurs bilaterally toward the sagittal sinus, and using hot water irrigation, muscle and fascia implants, a reasonable degree of hemostasis seemed to have been obtained. The patient, however, did not show any improvement and expired overnight. Autopsy permission was granted, and it revealed that large veins on either side of the sagittal sinus had been completely sheared off, leaving apertures like portholes in the sagittal sinus.

For the reason so dramatically and tragically illustrated in Case II, it is well, as with brain abscesses, to wait a time when possible, and not to take action, especially early, until one is certain that the die is cast and escape impossible. Case III illustrates a somewhat rare but not impossible example of spontaneous remission.

**CASE III**—This 26 year old patient was struck on the head with a packing case, was not knocked unconscious and continued to work, but in a period of twelve to fifteen hours he developed such a severe headache that hospitalization was deemed necessary. This was done and the patient continued to lie in bed without displaying any objective localizing neurologic signs. A lumbar puncture performed on the fifth post-traumatic day yielded xanthochromic fluid under the markedly elevated pressure of 500 mm. of water. I saw the patient two days following this and a second puncture was performed, yielding fluid which was still xanthochromic but in less degree and the pressure of which was 250 mm. At the time of my visit the patient complained of headache and stiff neck, but there were no neurologic findings whatever except for some slight engorgement of the optic fundi.

The patient improved gradually, and a spinal puncture done on the twelfth post-traumatic day yielded very faintly xanthochromic fluid under a pressure of 200 mm., and another puncture done five days later yielded clear and colorless fluid under the slightly high normal pressure of 170 mm. of water.

The patient continued to improve rapidly, and when last heard from was perfectly well and without disability.

Case IV is included in order to emphasize that we should not, in medicine, allow ourselves in our wish for simple explanations to be car-

ried to the absurd. It is obvious from contemplation of the manner of formation of subdural hematomas that they are dynamic and not static lesions. Symptoms from them increase, and I often oversimplify to medical students by saying that "patients with subdural hematoma are almost always either dead or operated upon within six months." Yet a certain number of cases are seen by me each year, some with medicolegal complications, in which this diagnosis has been made and insisted upon by some well-meaning physician, as long as three to five years after the alleged etiological trauma. I would say the case to follow is an average example.

CASE IV.—This patient, a 50 year old wife of an accountant had been in an automobile accident sixteen months before she was referred to me with the diagnosis of subdural hematoma, this being based upon a history of persistent headache, positional dizziness and generalized lassitude. At the time of the injury the patient had been rendered unconscious for a period of two hours, and had remained in the hospital for six weeks in the small town in which the accident happened. Following her return to her home in Chicago, the patient remained in bed and had a practical nurse for several weeks subsequently. She then began gradually to get up and about but she developed a marked fear of any strenuous activity, either mental or physical, because this apparently increased the discomfort, and as a result lived as a semi-invalid. This state of affairs continued until a year had elapsed, after which time symptoms began to increase slightly and the patient spent considerable time in bed. She had passed the menopause five years previously. She had no children, and her husband seemed to be a somewhat oversolicitous type. The patient had been examined by a number of physicians and had been out of the city to a couple of large medical centers before being referred to me.

In view of the long history and the obvious fact that the patient and her husband needed to be satisfied in their minds that no serious surgical condition was developing, the patient was admitted to the hospital. She complained considerably and required a good deal of analgesic and sedative medication. Complete neurologic examination and examination of the optic fundi were all normal. X-ray plates of the skull revealed no abnormality and no evidences of fracture, old or recent, and the pineal body was calcified and lying in the normal position in the midline. Lumbar puncture yielded clear, colorless fluid under the low normal pressure of 110 mm. of water, in which all findings were completely within normal limits.

It was explained to the patient and her husband, as well as to the referring physician, that no space-occupying lesion, such as a subdural hematoma, seemed to be present, and that the symptoms, which for a time had undoubtedly been genuine following the patient's moder-

tely severe head injury were now rapidly approaching an entirely functional state. The matter of encephalography was also discussed, and all concerned were informed by me that there was some psychological risk in performing this procedure on this type of patient since, if it did not help considerably, it might very likely do the opposite. Because nothing very constructive with regard to management of the case could be reasonably expected with this procedure, it was decided to abjure it. After a thorough medical elimination of other possible causes of headache, psychiatric consultation was called and at last hearing was still proceeding intermittently, several months after I saw the case, with a moderate degree of success. The patient at first resented the thought that her complaints might not be organic in nature.

My final protocol concerns a kind of experience which, for all our vigilance, occurs with distressing regularity each year. However, such an experience does have a three-fold good effect. First, it helps to keep us humble. Second, it reminds us to think long and carefully before resigning ourselves to inactivity in the face of impending death and bolsters our morale when we advise stricken families to have a simple exploration, even when we know how high are the probabilities of fruitlessness. (This does not mean that we, for instance, advise decompression for some such lesion as tuberculous meningitis, but only that no matter how strongly we feel we will encounter a glioblastoma in a patient with a rapid history of an expanding lesion, our consciences must demand confirmation, for sometimes we are wrong.) And third, providence seems to balance those cases we neglect from ignorance with others, equally unsuspected and unexpectedly hit upon, in the face of apparently overwhelming odds.

CASE V.—This patient, a man of 65, had been an enigma at the hospital in which he was a patient. He had been seen by several leading neurologists, and opinions were evenly divided as to whether he suffered from some diffuse encephalitic process or a malignant glioma of the brain. Several spinal punctures had been performed, the dynamics chemistry, serology and cell count of which had been normal, x-ray plates of the skull were also normal except that the pineal body, which was in the midline, was interpreted as being slightly depressed. When I saw the patient, he had been ill in the hospital for about two weeks and had been in coma for several days. There was a complete right hemiplegia and a complete aphasia had existed prior to the onset of coma. The blood pressure was low, and spinal fluid pressure on punctures had never shown any increase in intracranial tension, as stated above. The lesion had been progressive, as far as the history was concerned, over a number of weeks. The family gave no

history of any antecedent history, therefore, in view of the rapid progress of the lesion, I felt it was probably a malignant infiltrating glioma, which was destroying brain tissue rather than pushing it to one side and creating edema and, as sometimes happens with such cases, there was no increase in intracranial pressure and no great pineal shift

Following my visit the patient remained in a precarious condition and finally expired in about a week. Autopsy permission was obtained and a bilateral subdural hematoma was disclosed, which was larger over the left hemisphere than over the right. The family then remembered that the patient about two months previously had come home from his work, which was that of laundry man, and had complained that he had been in a minor automobile collision and had been thrown against the metal roof of the cab of his delivery truck. In view of the pathologic nature of the lesion, double indemnity was awarded in the case of this death on the ground that the lesion was necessarily post-traumatic, whether the original trauma had ever been officially reported or not.

#### SUMMARY

I have attempted to make clear the manner of formation and the clinical manifestations and vagaries of this interesting and not uncommon condition. Bear in mind the surgical pathology of its development, the dynamic nature of its progress and the paradox of its appearance in mild rather than severe head trauma. Only thus can we conscientiously discharge our duty to our patients, and, we hope, maintain a high diagnostic batting average. It is worth it.

## THE RELIEF OF FACIAL PAIN

A LARI WALKER, M.D.\*

A DISCUSSION of facial pain based upon the location of the pathologic change is not entirely satisfactory from the clinical standpoint. The etiology of too many cases of pain in the face is still obscure. A much more valuable classification is based upon the description of the pain which frequently is so typical that a clinical diagnosis may be made from the history. This is particularly true when considering the surgical relief of facial pain, for certain trigeminal neuralgias with distinct clinical characteristics are amenable to operative procedures, whereas other neuralgias of the face clinically differing from the first type only in the description of the pain are not affected or may even be aggravated by such surgical therapy.

### TRIGEMINAL NEURALGIA†

**Symptomatology**—Trigeminal neuralgia is a distinct clinical entity characterized by severe paroxysmal pain confined to one, two or three divisions of the trigeminal nerve without sensory or motor disturbances in the face. The paroxysm is described as a sharp, shooting, darting, stabbing, burning, cutting, tearing, grinding, boring or jabbing pain in the teeth, jaw, cheek, eye or temple lasting only a few seconds. The spasmodic nature of the disease with practically complete freedom between the crises except for perhaps a slight soreness in the face is an essential feature of the condition (Fig. 22).

Initially the pain usually occurs spontaneously in the upper or lower jaw. Commonly it is referred to a tooth, which though it be pronounced healthy by the dentist, is finally removed at the insistence of the patient. Unfortunately, relief from such measures is not forthcoming, for dental disease is not an etiologic factor in this condition. The pain gradually increases in frequency and radiates over a wider area to the cheek, tongue, lips or lower jaw. With increasing paroxysms the pain tends to spread, although for years it may be confined

---

From the Division of Neurological Surgery, the University of Chicago Clinics, Chicago.

\* Associate Professor of Surgery (Neurosurgery), University of Chicago School of Medicine.

† This condition is also called *trifacial neuralgia*, *tic douloureux*, *epileptiform neuralgia*, *Fothergill's disease*, *neuralgia major* and *prosopalgia*.

to one division of the trigeminal nerve, usually the third, occasionally the second and rarely the first

**Trigger Zones**—The patient soon recognizes that a paroxysm may be set off by mechanical irritation of a small area of skin of the face or mucous membrane of the mouth. Merely touching these "trigger zones" or "dolorogenetic areas" will induce an agonizing paroxysm. Usually the trigger zones are situated about the lips, the nose or on the alveolar margins of the jaws. The pain induced by stimulation of



Fig 22—An artist's phantasy depicting the horrors of trigeminal neuralgia (From a lithograph by Alexander Ver Huell)

the trigeminal nerve may be referred to areas quite distant from the situation of the trigger zone, even to a completely anesthetic area. Thus the trigger zone may be in the upper lip, while the pain is in the forehead or lower jaw. Even a breeze blowing on the face may be an effective stimulus so that the patient wears a shawl. Washing the face may induce such agonizing pain that dirt is allowed to become matted on the cheek. The irritating stimulus need not be exogenous. Chewing, swallowing, or movements of the tongue may be quite adequate to bring on a paroxysm of pain. As mute evidence of this, in

patients suffering from neuralgia of the third division, the affected side of the tongue may be markedly furred as compared to the clean surface on the other side. The agony of eating is such that these sufferers rapidly lose weight due to inanition and dehydration.

**Diagnosis**—The history is practically pathognomonic of the condition—indeed, since there are no constant abnormal neurologic or physical findings, the diagnosis must be based upon the history. The condition is characterized by remissions which may last months or even years. Not infrequently during the summer or winter the patient is free of pain, only to suffer again with the change of weather.<sup>31</sup> Strangely enough the right side of the face is affected more frequently than the left. The condition occurs more commonly in the female than in the male, but is almost invariably found in the latter half of life. Occasionally it is encountered in a young individual, but in such cases one is always suspicious that it is symptomatic of another intracranial condition. In 2 to 5 per cent of cases<sup>9, 14</sup> the condition occurs on both sides of the face, usually not simultaneously.

**Symptomatic Trigeminal Neuralgia**—Occasionally facial pain identical with that of *tic douloureux* may occur as a manifestation of another disease of the nervous system. Paroxysmal facial pain is encountered in *multiple sclerosis* more frequently than the chance coincidence of the two diseases. A plaque in the spinal root of the trigeminal nerve is present in some of these cases, and is thought to be responsible for the pain. *Syringomyelia* or *syringobulbia* may also have, as a symptom, attacks of facial pain presumably due to involvement of trigeminal nerve centers by the syrinx. Another disease in which typical trigeminal neuralgia may appear as a symptom is *tabes dorsalis*. One might consider the facial *tic* as a lightning pain but coincident pains in the extremities are infrequent. Rarely, one of the first manifestations of a *neoplasm in the cerebellopontine angle* will be typical paroxysmal trigeminal pain. Symptomatic trigeminal neuralgia usually may be clearly differentiated from the essential variety by the presence of neurological changes and in particular by sensory disturbances in the distribution of the fifth nerve. Such alterations in nervous function in a patient suffering trigeminal neuralgia should lead one to search carefully for an intracranial lesion.

**Pathogenesis**—The pathological basis of trigeminal neuralgia has not yet been adequately established. Early it was assumed that the pain was related to vascular disturbances in the gasserian ganglion. Since the disease occurs predominately in older individuals who are likely to have moderate or severe arteriosclerosis, one would expect to find vascular changes in and about the gasserian ganglion. However such



alterations are no more pronounced in patients suffering from trigeminal neuralgia than in patients of the same age group who die of other diseases. Moreover, many individuals suffering from trigeminal neuralgia have no evidence of arteriosclerosis or other vascular disease in or about the gasserian ganglion. It therefore seems difficult to give credence to this theory of the pathogenesis of trigeminal neuralgia.

It has been suggested that aberrant vessels passing across the trigeminal root between the pons and gasserian ganglion or sclerotic plaques in such vessels might irritate the nerve root. Dandy<sup>3</sup> has particularly emphasized this view since in the cerebellar approach for the relief of trigeminal neuralgia he is able to visualize the structures about the trigeminal nerve better than those operators who perform the classical retrogasserian neurotomy. In 1932 he stated<sup>2</sup> that in patients with trigeminal neuralgia he had found a 12.5 per cent incidence of vascular abnormalities and a 5 per cent incidence of otherwise asymptomatic tumors in the cerebellopontine angle. Seven years later<sup>3</sup> he reported that the incidence of tumor was still 5 per cent but that vascular anomalies were present in nearly all other cases. Most neurosurgeons believe that in the vast majority of cases of trigeminal neuralgia no gross pathological factor is known.

Lewy and others<sup>9, 20</sup> suggested that pathologic changes in the thalamus were the basis of trigeminal neuralgia. However, this view has not been generally accepted, largely due to the fact that significant thalamic disease has not been found in the brains of patients who have suffered from trigeminal neuralgia.

#### TREATMENT

**Principles**—The therapy of this condition is directed to a diminution of afferent impulses reaching the central nervous system through the affected trigeminal nerve. This may be accomplished by drugs decreasing the conductivity of the trigeminal nerve, by blocking the trigeminal nerve or by anatomical interruption of the fibers of one or more branches of the trigeminal nerve. Although dental, sinus and other local facial lesions are not considered etiologically related to trigeminal neuralgia, it is advisable from the general medical standpoint to eliminate any infection in the mouth or sinuses. Sometimes such procedures will bring about a rather long-standing remission of the trigeminal pain. It should be emphasized, however, that such treatments should be made for the purpose of eliminating actual sinus or dental disease and not primarily for the relief of trigeminal neuralgia per se.

## Medical Management

**Drugs.**—Medical management in early and mild cases may give slight relief. Recently Davidoff<sup>2</sup> has revived the old treatment suggested by Hutchinson, namely, the administration of *ferrous carbonate* in doses of 60 grains a day. The persistent use of this therapy is said to relieve trigeminal neuralgia but my personal experience with this medication is disappointing.

*Thiamine hydrochloride* has been suggested as a means of treating trigeminal neuralgia.<sup>1</sup> The results of this therapy when critically reviewed are not encouraging. It is said that the treatment must be given for several months before results can be expected, but knowing the tendency of trigeminal neuralgia to undergo spontaneous remissions, it seems likely that such remissions have occurred during the treatment of those patients who were said to have received benefit from vitamin B<sub>1</sub> therapy.<sup>25</sup>

Once the paroxysms are established, medication is of no significant or lasting value. To tide the patient over a crisis until more adequate therapy can be administered, *trichlorethylene* may be of temporary value. The predominant effect of this drug on the trigeminal nerve was recognized during the first World War when occupational exposure to it was found to produce a numbness of the face. The usual method of treatment is to pour 15 or 20 drops of trichlorethylene on a handkerchief in a cone of paper. The patient, sitting or lying to avoid falling should lightheadedness develop, places his face over the open end of the cone and inhales until the odor has disappeared. If the inhalation is taken a few minutes before a meal, eating may be possible without discomfort. The patient should be warned that the drug should not be inhaled oftener than three to four times a day, for more frequent inhalations may produce an intoxication. One patient suffering from a severe trigeminal neuralgia was brought into the hospital in a comatose state. Her husband stated that because of the severe pain she had inhaled two or three 4-ounce bottles of trichlorethylene within a day or two gradually becoming more and more stuporous. It was several days before she recovered from her intoxication. While narcotics will relieve the pain, their administration is not advisable owing to the danger of addiction. This is particularly to be emphasized since such treatment may lead to a more difficult problem than the original complaint.

**Alcohol Injections.**—For all patients whose pain is severe, the treatment of choice is interruption of the trigeminal nerve or its branches. This may be done by an alcohol injection of the peripheral nerves

the gasserian ganglion, or by surgical section of the root. Which of these procedures should be carried out is a question to be decided upon by the physician in each individual case. Alcohol injection produces a temporary paralysis of the nerve, with simultaneous return of the function and usually of the pain in three to eighteen months. Occasionally a gasserian ganglion injection will last many years<sup>14</sup>. If the individual has mild or infrequent paroxysms or shows neurotic tendencies, it may be wise to inject alcohol into the involved division or peripheral nerve to determine the patient's reaction to the resulting paresthesia. Not only is the individual given an opportunity to decide whether the numbness is preferable to the pain, but the surgeon may determine that a retrogasserian neurotomy will give relief. For this reason some operators are of the opinion that all patients should have a preliminary injection before surgical section. However, since the injection is not without pain or danger, a primary retrogasserian neurotomy is advisable in patients whose general physical condition suggests a life expectancy of more than five years and who are suffering severe paroxysms at relatively frequent intervals.

The following case illustrates the value of a preliminary alcohol injection.

E. P., a 52 year old locomotive fireman, was admitted to the University of Chicago Clinics on August 2, 1943. He complained of an aching, jerking pain in the left cheek of three years' duration. About one year after the onset of the symptom the patient consulted a dentist who, finding a "white spot" over the premolar teeth, extracted all his upper teeth. Relief not occurring, all the lower teeth were removed—but the pain persisted. In March 1943 the pain became so severe that he was unable to sleep at night. He was given a series of 22 "shots" in the right cheek, which relieved his pain for two weeks, but when it returned it was more severe than ever.

The pain was a constant ache fairly well localized to the left cheek near the temporomandibular joint. For periods of ten minutes to two hours it became sharper and jerking, after which it returned to a persistent ache. While it occurred at any time of the day or night, it was often brought on by talking, eating, wearing a denture or lying on that side of the face. Because of the difficulty in eating and sleeping, the patient lost 20 pounds in weight.

The past history and functional inquiry were not contributory.

The patient was a thin, edentulous male, whose physical examination revealed no abnormality. His memory was not good, but he blamed this upon loss of sleep. Neurologic examination otherwise was normal except for a slight hypalgesia over the left upper lip and cheek.

The diagnosis in this case was not clear. The patient's description of

his pain was not that of a typical trigeminal neuralgia. The exacerbations of severe pain brought on by talking, eating and so forth suggested tic douloureux, but the constant ache made the condition atypical. For that reason an alcohol injection of the nerve was advised as a therapeutic test.

On August 3, 1943 after anesthetizing a small area of the cheek, a needle was inserted through the foramen ovale to the gasserian ganglion. After injection of 0.5 cc of 1 per cent novocaine the skin innervated by the second division became anesthetic and following another injection of 0.5 cc of novocaine that supplied by the third division became hypesthetic. An injection of 1 cc of absolute alcohol was made and another injection of 0.5 cc after the needle had been withdrawn 1 cm. The patient experienced a burning sensation in the face as the injection was made.

On the following morning the sensory disturbances were less pronounced and largely confined to the area of innervation of the third division. The patient's pain was less, so he was discharged to return in one week. However, his pain returned and on August 6, 1943 another injection was made in the left gasserian ganglion, 1.2 cc of alcohol being used. An anesthesia of the second and third divisions was obtained. His severe pain was immediately relieved. One year later, August 2, 1944 he returned. His face felt numb and he had some paresthesias in the face, but none of the former severe pains. He still had practically a complete anesthesia of the second and third divisions of the trigeminal nerve with paralysis of the masseter and temporal muscles. He had gained weight and felt quite well.

This case illustrates the value of alcohol injection. Although the history of this patient was not quite typical of true trigeminal neuralgia, he obtained almost complete relief from interruption of the function of the fifth nerve. If this patient's pain returns, a retrogasserian neurectomy is contemplated. Such unusual cases of trigeminal neuralgia occasionally are seen. A block of the fifth nerve is necessary to establish the diagnosis and to be certain that nerve section will relieve the pain. Not infrequently the severe paroxysms may be abolished leaving the background paresthesias still present.

The alcohol injection may be made into a peripheral branch of the trigeminal nerve at the supraorbital, infraorbital or mental foramen, depending upon the location of the pain. If more than one division is involved, the gasserian ganglion must be injected. While it is possible to inject the third division alone at the foramen ovale, it is impossible to inject either of the other divisions or any two other divisions selectively with certainty. Injection at the foramen rotundum is too hazardous for routine use. One must then consider the probability that

the injection of the gasserian ganglion will produce a complete paralysis of the trigeminal nerve with anesthesia of all three divisions

The injection must be made when the patient is awake so that the position of the needle may be determined with certainty—by the injection of 0.5 cc of 1 per cent novocaine. Unless an anesthesia of the area innervated by the injected nerve is obtained, alcohol should not be used, for there is danger of injecting intracranial structures which may produce serious sequelae. Blindness, oculomotor paralysis and unilateral deafness are not unknown as sequelae of attempted alcohol injections of the gasserian ganglion. If the desired root or ganglion is not struck after three or four attempts, it is usually better to desist and attempt another injection at a later date since not only is the patient hurt by the attempts, but the novocaine injected infiltrates slowly into the tissue and may reach the nerve thus producing anesthesia when the tip of the needle is too far away for an alcohol injection to be effective. Usually 1 cc of absolute alcohol is all that is required for a good block of a peripheral nerve or the gasserian ganglion. In spite of the preliminary novocainization there is considerable burning pain as the alcohol reaches the nerve fibers. This disappears within a few minutes leaving the area anesthetic. Before carrying out the procedure it is frequently advisable to give the patient  $\frac{1}{4}$  or  $\frac{1}{6}$  gr (0.015–0.010 gm) of morphine. If the first division is rendered anesthetic by the injection, the cornea should be protected by an eyeshield as described later in this paper.

### Surgical Methods of Treatment

Fifty years ago the surgical therapy of trigeminal neuralgia was largely confined to methods of sectioning or stretching the peripheral branches of the fifth cranial nerve.<sup>10</sup> At about that time it was recognized that such procedures were quite temporary, for Horsley<sup>15</sup> and Rose<sup>20</sup> were suggesting operations upon the trigeminal root and ganglion. Unfortunately the surgical technic then was not developed to a sufficiently high level that such operations could be performed safely. Surgical procedures upon the peripheral branches have been largely discarded except for the avulsion of the supraorbital nerve. This is still carried out in selected cases of first division pain when the condition of the patient precludes a more serious operation, or in cases in which the possibility of keratitis is to be avoided even at the risk of recurrence of the pain.

**Classical Retrogasserian Neurotomy**—The classical retrogasserian neurotomy (Spiller-Frazier operation) remains the safest and most certain method of surgical treatment of trigeminal neuralgia. The mortality

from this procedure is low (less than 1 per cent) and the morbidity slight. Ordinarily the period of hospitalization is not more than five or six days. It is possible selectively to cut any desired division or divisions of the trigeminal nerve and to leave intact the motor division. Thus, in the majority of cases, because the pain is confined to the lower part of the face, the first division of the trigeminal nerve is spared. If the section has been adequate complete relief of pain is obtained. Grant<sup>9</sup> reported 949 operations with complete relief of the pain in 942 instances. In the seven patients having no relief, it was assumed that the pain was not that of trigeminal neuralgia and that operations should not have been performed. Such an error in diagnosis might have been avoided by a preliminary injection of alcohol into the appropriate branch of the fifth nerve.

**OPERATIVE RESULTS**—The most extensive report upon the operative results of retrogasserian neurectomy is Grant's compilation<sup>9</sup> of the cases operated upon at Philadelphia the majority by the late Charles L. Razier. The figures presented here are based upon those data.

**Recurrence**—Following what was considered by the operator to be complete sensory root ablation the pain recurred in seven patients in the series of 359 cases (2 per cent). In the series of 590 patients in whom partial section was accomplished there were forty-four recurrences (7.4 per cent). In all but four of these cases the recurrence was in the first division which had been deliberately spared. Avulsion of the supraorbital nerve was sufficient to relieve thirty of these cases.

**Paresthesias**—Following retrogasserian neurotomy the majority of patients have little complaint referable to the anesthetic face. Approximately 13.8 per cent notice paresthesias, such as numbness, heat or cold, itching, drawing or twitching. In Grant's series 3.4 per cent had more severe paresthesias which were usually referred to as a burning itching pain. These paresthesias may develop immediately after the operation or occur at later intervals, but usually within the first year or two. Some of these patients will become so accustomed to the paresthesia that it does not bother them but the majority continue to complain of paresthesias of greater or lesser severity. The relief of such disturbances is not very satisfactory. Secondary operations upon the sensory root do not relieve the pain nor has sympathetic surgery given good results.

**COMPLICATIONS**—**Keratitis**—Following complete section of the sensory root, keratitis results in approximately 16.7 per cent of cases and in approximately 10 per cent of these cases enucleation of the eye is necessary to control the infection. Following subtotal section of the root the danger of keratitis is much less—approximately 4.4 per cent—

and the severity of the keratitis is also less. The keratitis may result from involvement of the cornea by the herpes which frequently develops about the lips after operation or more commonly from trauma due to painless scratching of the cornea by dust or cinders lodging in the conjunctival sac. To avoid such a complication the patient should be advised to keep the eye protected by a shield attached to the rim of spectacles and snugly fitted to the contour of the orbit. To prevent fogging the lens, small perforations may be made in the shield or the glass treated by "antifrost." The patient should be advised to wash out the eye morning and night with a boric acid solution and to report to his physician if the slightest corneal injection develops. Unfortunately, some patients do not take this advice seriously. I had one patient who, instead of washing the eye out morning and night, would dab a piece of cotton into the solution and wipe it across the cornea. By such trauma he shortly developed a keratitis. If simple irrigations do not relieve the keratitis, it is advisable to suture the eyelids. Under no circumstances should a cotton pad be placed over the eye, for these patients are apt to open the eyelids, allowing the cotton to rub painlessly on the anesthetic cornea. Castor oil dropped into the conjunctival sac morning and night will keep the cornea moist.

*Facial Paralysis*—Facial paresis occurred in 34 per cent of Grant's cases. The majority of patients with this complication recovered completely within six months, but a few did not recover. It has been suggested that the cause of the facial paralysis may be either hemorrhages in the pons due to an avulsion of the sensory root of the fifth nerve or damage to the petrosal nerve or vein by stripping the dura mater from the floor of the skull. Gardner and Babbitt<sup>7</sup> have noticed hemorrhages in the middle ear in certain cases complicated by facial paralysis.

*Other Complications*—Rarely the third, fourth or sixth cranial nerve may be damaged during a retrogasserian neurotomy. Since many of the patients are elderly, it is not surprising that occasionally a hemiplegia due to thrombosis or hemorrhage develops as a complication. Such vascular accidents are the usual cause of the rare fatality which occurs following the operation. In a few cases cerebral anemia due to a rapid fall in blood pressure during the operation with the patient sitting may produce symmetrical areas of necrosis in the paracentral region and later death from pneumonia. Rarely trophic disturbances develop in the anesthetic area of the face. Usually these are the result of chronic irritation of the skin or mucous membrane. The lesion is usually a necrotic area lined by granulating tissue. It responds poorly to any type of therapy (Fig. 23).

**Posterior Retrogasserian Neurotomy**—Dandy<sup>2 3 4</sup> has utilized a sub-cerebellar approach for sectioning the posterior root of the trigeminal nerve, for he claims that following partial section by this route there is never corneal disturbance never loss of the motor branch, little, if any, loss of sensation in the face, rarely facial paralysis and severe hemiplegia. This method in the hands of a highly skilled surgeon would appear to have definite advantages but many neurological surgeons consider it technically more difficult and potentially more



Fig 23—Trophic disturbances about the nose of a patient following alcohol injection of the gasserian ganglion for the relief of tic douloureux. The patient was constantly wiping the nose on account of paresthesias.

dangerous than the classical retrogasserian neurotomy. The preservation of sensation in the face with complete relief of pain and infrequent recurrence (2 per cent) is much in favor of the operation, for it prevents the disagreeable paresthesias in the numb face. Hyndman<sup>17</sup> finds that he can obtain equally good results with little or no sensory loss using the subtemporal approach and only sectioning a part of the posterior root of the trigeminal nerve. These observations suggest that the trigeminal root undergoes a rearrangement of fibers as it passes



from the gasserian ganglion to the pons so that the divisions are no longer separately or isolatedly grouped

**Medullary Tractotomy**—With a view to eliminating paresthesias in the face by sectioning only the pain fibers of the fifth cranial nerve, Sjoqvist<sup>27</sup> in 1938 introduced medullary tractotomy as a means of relieving facial pain. The operation is carried out by a suboccipital approach and the descending tract of the trigeminal nerve is sectioned near the level of the obex (Fig 24). Olivecrona<sup>24</sup> has reported upon the largest series of cases operated upon by this method. In thirty patients having unilateral trigeminal neuralgia he performed a medul-



Fig 24—A cross section of the medulla oblongata through the level of medullary tractotomy showing the area of the incision

lary tractotomy with no deaths. In eighteen cases an analgesia of the face resulted, in nine a hypalgesia and in three cases no sensory loss was detectable. The pain was relieved immediately in most cases but eight patients had a recurrence of pain, two of whom had a subtotal or complete analgesia of the face. The disturbances in appreciation of temperature did not parallel the pain loss. Some impairment of touch was usually detectable. In two-thirds of the cases disturbances of equilibrium were present, though usually transient. Grant and his co-workers<sup>10 11 12 29 30</sup> had previously emphasized this complication in their series of fifteen cases. Both Grant and Olivecrona found that the

patients complained of paresthesias, in Olivecrona's series 16.7 per cent had such disturbances. But more important, eight of Olivecrona's series had unilateral paralysis of the vocal cords. Herpes labialis and keratitis were reported in Olivecrona's series. In four of Grant's patients hiccoughs were a troublesome, though temporary, complication. Olivecrona operated upon four patients suffering from bilateral trigeminal neuralgia, although in only three cases was the operation performed bilaterally. In the one unilateral and one bilateral case little or no relief was obtained but in the other two bilateral cases good results followed the operation.

Olivecrona's report appears to be fairly representative of the results obtained by other operators on smaller series of cases. Almost all neurological surgeons who have tried the procedure have had excellent results only in the majority of cases. For this reason both Grant and Olivecrona conclude that it is not ideal as a routine procedure for trigeminal neuralgia but that it has a definite place in the treatment of selected cases.

#### ATYPICAL TRIGEMINAL NEURALGIA

Atypical trigeminal neuralgia is a designation used to include many varieties of facial pain, which differ in some clinical respects from trigeminal neuralgia and which have no known etiology. They are frequently referred to as psychalgias because of their association with psychoneurotic manifestations. Although this type of pain may be as bitterly bemoaned as that of *tic douloureux*, frequently the calm mien of the patient seems to belie his complaints. However, in some cases the pain is so distressing and annoying that the patients threaten suicide, become drug addicts or markedly psychopathic.

The main distinction between this group of facial neuralgias and typical trigeminal neuralgia is in the *duration* of the pain. While in *tic douloureux* the pain is paroxysmal, lasting only a few seconds, in atypical trigeminal neuralgia it tends to persist for relatively long periods of time, although there may be severe exacerbations for a few seconds or minutes. The description of the pain in the two conditions may be similar. In a typical neuralgia Glaser<sup>8</sup> found that a dull aching pain is the most common description of the sensation, occurring in approximately 37 per cent of the cases, but many patients complain of a burning, throbbing, shooting, sharp, boring, drawing or pulling feeling in the face, which, it will be observed, is quite like the description of the pain in true trigeminal neuralgia. Less frequently the distress is described as gnawing, sore, toothache, knifelike, pricking, beating, needle-like, gripping, bugs-creeping, electric, tingling, lightning,

bursting, nagging, stinging, smarting, itching or tearing. These sensations persist for minutes, hours, or on occasions are present to a certain degree constantly for days. They are aggravated by cold, fatigue, heat, draught, menses, excitement, eating, brushing teeth, talking, worry and other irritating factors.

It will be noticed that the most frequent factor aggravating the pain is cold, which also initiates the paroxysms of trigeminal neuralgia. It is therefore not surprising that the atypical and typical trigeminal neuralgias may be confused at times, especially if a critical history is not taken. This is particularly apt to occur, for patients suffering atypical trigeminal neuralgias are quite susceptible to suggestion, and the inquiring physician stressing the symptoms of trigeminal neuralgia might easily induce them in such cases.

Not infrequently facial pain is associated with sympathetic phenomena, such as lacrimation, edema of the face, corneal and conjunctival injection, salivation, nasal discharge, flushing of the face, and nausea and vomiting. Somewhat more than half of the cases have such sympathetic phenomena associated with the pain. Rarely do the sympathetic phenomena occur without pain. The location of the pain does not necessarily predicate the sympathetic discharge. In other words, the patient may have pain in the lower jaw and lacrimation or conjunctival injection. In many cases the onset of the pain is referred to a specific incident, such as extraction of a tooth, a wound of the head, or some unusually intense emotional experience.

The location of the pain varies a great deal in these cases, and even in the individual case, but it differs from the typical trigeminal neuralgia in that it is never quite so localized or confined to one or two divisions of the trigeminal nerve. Usually it involves the side of the face, particularly the cheek and eyeball, and extends backward above and behind the ear into the side of the neck. It may, however, be more or less confined to the cheek, the eye, the cheek and eye, or occasionally to the lower jaw, but usually it radiates posteriorly in the direction of the ear and temporal region. In a few cases the pain is bilateral, extending across the midline to the opposite side of the face. The lips are most commonly said to be involved by such pain, the disturbance being felt in the perioral region on both sides and in the cheek and ear on one side.

In the majority of these cases, psychiatric examination reveals personality characteristics suggesting a psychoneurosis and the pain is often said to be psychogenic in origin. Why the neurotic manifestation takes the form of facial pain is not clear, and even a detailed analysis of the case is not always elucidative in this regard.

## SYMPTOMATIC FACIAL PAIN

Many organic diseases of the head will give rise to facial neuralgia, some through the mechanism of referred pain but others due to direct irritation of the trigeminal nerve. Among the more common conditions causing pain in the face are sinus infection, dental abnormalities, ocular disorders, neoplastic disease and vascular disturbances.

**Sinus Infection as a Cause of Facial Pain**—The pain resulting from infection of the air sinuses is usually dull and aching in character. Rarely are there acute paroxysms such as one encounters in true trigeminal neuralgia. Not infrequently the pain is aggravated in the afternoon as the sinuses become filled with mucus. The history of a previous cold and the presence of a nasal discharge and local tenderness over the sinus aid in the diagnosis. Poor transillumination and roentgenologic evidence of clouding usually confirm the diagnosis. The paroxysmal pain of trigeminal neuralgia is rarely, if ever, an accompaniment of sinus infection.

**Dental Abnormalities**—Without question the teeth are considered by the laity to be the usual cause of facial pain and yet actually they are rarely the responsible agent. Dental caries, gingivitis and apical abscesses do give rise to facial pain, which may be limited to the diseased tooth or referred to a division of the trigeminal nerve. Usually the discomfort is a persistent ache accompanied by local soreness aggravated by biting or eating. Impacted wisdom teeth may produce a chronic ache in the side of the face but rarely do they give rise to a typical trigeminal neuralgia. The ache is usually referred to the region of the ear and may be aggravated by chewing or movements of the jaw. Malocclusion of the teeth associated with temporomandibular arthritis does induce a severe pain in the side of the face, which occasionally has sharp agonizing exacerbations. This syndrome, like those previously mentioned, usually consists of a persistent pain that is present most of the time, aggravated by eating, chewing and movements of the jaw. Upon examination there may be an audible creaking of the joint on auscultation and tenderness on pressure. Dental appliances to relieve tension upon the articulation usually suffice to alleviate the discomfort.

The following case illustrates a rare dental complication.

I L., a 36 year old housewife, was admitted to the University of Chicago Clinics April 7, 1943, complaining of severe pain in the left mandible. In 1939 she had a block of the inferior alveolar nerve for removal of an impacted wisdom tooth, following which the lower jaw remained numb and the face became painful. The numbness persisted, but the pain varied considerably in intensity. About two y

before admission the pain became severe again and was not relieved by local dental procedures. The pain continued and about a month before admission an alcohol injection was made in the lower jaw. This therapy, however, aggravated the pain. It was described as a constant ache with sharp stabbing exacerbations radiating into the temple. In general the pain centered about the lower jaw but it was present in the cheek and the temporomandibular articulation with radiation to the left ear. Codeine was necessary for relief.

Her past and family history revealed nothing relevant to the present complaint except that she had had many previous illnesses, dysmenorrhea, nervous exhaustion, heart "strain," and recurrent periods of depression initiated by strenuous emotional situations.

Physical and neurologic examinations were quite normal except for the findings referable to the left side of the face and jaw. Over the distribution of the third division of the left trigeminal nerve a hypesthesia to pinprick and cotton was present, but deep pressure in this region was painful. The remaining teeth were in good repair but there was a scarred area in the posterior portion of the left lower alveolar arch, at the site of the removed wisdom tooth, which was tender to touch or pressure. Any manipulation of this area caused severe pain.

The patient was seen by dental surgeons, who found no dental abnormalities but considered the scarred alveolar ridge an adequate source of her trouble. The mandibular nerve was blocked by novocaine, with complete relief of pain and abolition of the sensitivity of the scar. She was then able to bite well, a process that formerly was quite painful.

Roentgenograms of the temporomandibular joint showed no abnormality. Occlusion was adequate.

Section of the lower divisions of the left trigeminal nerve was advised, but the patient wished to consider it since she was apprehensive of the operation and its sequelae.

On June 6, 1943, she returned because the pain was increasing and she was forced to take 3 grains of codeine daily for relief. Her clinical findings had not changed in the interim.

On June 8, 1943, the patient was anesthetized by intravenous sodium pentothal. A vertical incision was made in the left temporal region and carried through the temporal fascia and muscle. The bone was perforated, and the opening enlarged by rongeurs. The dura mater was elevated from the floor of the middle fossa, until the foramen spinosum was identified. It was plugged by a small piece of cottonoid and the middle meningeal artery was cut. The dura mater was then separated from the sheath of the third division of the trigeminal nerve. An incision was made in the sheath posterior to the gasserian ganglion and the sensory roots of the third division were avulsed. A few fibers of the second division were removed but the motor root, readily identified, was left intact. Moderate oozing was controlled by muscle

staples The muscle, fascia and skin were then closed in anatomical layers by interrupted black silk sutures

The patient had an uneventful convalescence and was completely relieved of pain The alveolar margin was no longer tender and painful The area innervated by the third division of the trigeminal nerve was completely anesthetic as well as the greater part of that supplied by the second division The left masseter muscle contracted feebly The patient was discharged from hospital on the fifth postoperative day

She has been seen on two subsequent occasions, the latest one February 23, 1944 At that time she had no pain in the face or jaw, but a pressure sensation about the left ear She had been worrying a great deal and suffered headaches and insomnia There was still an anesthesia of the area supplied by the third division of the left trigeminal nerve and marked hypalgesia of the second division The masseters both contracted strongly She was well satisfied with the result of the operation

**Vascular Disturbances**—Another type of facial pain that occasionally tends to be confused with trigeminal neuralgia is the so-called *histamine headache*, which is presumed to be due to vascular disturbances<sup>10</sup> The attacks occur usually at night or in the evening with a peculiar regularity and are associated with profound flushing and lacrimation on the affected side Night after night the patient may be awakened at the same hour by a severe, throbbing, unilateral pain in the temple, cheek or eye The attack has a sudden violent onset, lasts thirty to sixty minutes, rarely longer, and subsides rapidly The carotid vessels may be tender during the episode There is no associated vomiting or visual hallucinations, and the affected patients rarely have a migrainous history Alcohol may precipitate an attack and the subcutaneous injection of histamine regularly induces it In some cases so-called "desensitization" by repeated small doses of histamine will relieve the attacks The syndrome in its pure form is so typical that it is readily recognized

Another type of probable vascular disturbance occurs in individuals subject to migraine, who will have attacks of severe pain in one side of the face lasting for hours and gradually disappearing The more gradual onset, longer duration of the attack and previous history of migraine serve to differentiate this condition from histamine headache and to indicate its nature

**Bony Involvement as a Cause of Facial Pain**—Occasionally small lesions of the frontal or temporal bone may be responsible for facial pain Thus osteomyelitis of the skull, luetic osteitis and epidermoid tumors may be the cause of localized head pain Usually the cause of

the trouble is recognized by roentgenographic examination of the skull. At times local tenderness over the area may be present.

**Ocular Origin of Facial Pain**—The discomfort produced by refractive errors is usually spoken of as a frontal headache, rather than as a pain. Its relationship to eye-strain is usually quite evident—although occasionally bouts of pain may occur apparently independent of the use of the eyes. Iritis and glaucoma may be associated with intense referred pain in the cheek and temple as well as the orbit, but the associated visual disturbance and ophthalmologic findings are usually sufficient to enable an accurate diagnosis.

**Intracranial Causes of Facial Pain**—Any lesion of the posterior root, gasserian ganglion or peripheral branch of the trigeminal nerve may give rise to facial pain. If the disease is peripheral to the posterior root the pain is usually of a constant character and may be referred to one or all of the divisions of the trigeminal nerve. Lesions along the root and pons are apt to induce paroxysmal pain as described under symptomatic trigeminal neuralgia. The condition may be differentiated from local disease in the face by the presence of sensory disturbances and subjective paresthesias.

*Tumors of the gasserian ganglion* early give rise to severe pain and numbness in the face.<sup>18</sup> The pain may be paroxysmal but some residual discomfort is usually present between attacks. These tumors are usually carcinoma extending from the nasopharynx but occasionally primary neurofibromas, meningiomas or epidermoids may be found.<sup>21</sup> Rarely a temporal lobe glioma will compress the gasserian ganglion producing pain.

*Herpes zoster of the gasserian ganglion* is not infrequent and may involve any one of the three branches of the trigeminal nerve. The history of such cases is usually typical. Severe pain and redness is present in one or all divisions of the trigeminal nerve, followed in two or three days by a vesicular eruption on the face. The vesicles gradually dry leaving a brownish scale. The pain usually recedes at about the same time but for several weeks the involved area may be hyperesthetic to the touch. Paroxysmal or persistent pain may continue for months. X-ray therapy will sometimes give relief for this type of pain. Retrogasserian neurotomy usually does not stop the pain although in a few cases relief is obtained. A Sjoqvist medullary tractotomy has been performed with fair results in one case.<sup>27</sup>

Occasionally one sees uni- or bi-lateral trigeminal neuritis as a manifestation of a generalized peripheral neuritis in the *Guillain-Barré syndrome*. The diagnosis is obvious, due to the accompanying manifestations of peripheral neuritis. A neuritis of one or both trigeminal nerves

occurs, presenting the clinical picture of facial pain, tenderness of the peripheral nerves especially at the supraorbital, infraorbital and mental foramina numbness of the face and impaired sensibility in the distribution of the trigeminal nerve. The etiology is usually indeterminate but occasionally a toxic agent such as trichlorethylene may be incriminated.

Along their course from the gasserian ganglion to their foramina of exit upon the face the branches of the trigeminal nerve may be involved by inflammatory, traumatic or neoplastic processes. Comment should be made of the fact that *intracranial aneurysms* may be responsible for facial pain. These vascular anomalies usually involve the trigeminal root between the gasserian ganglion and pons, at the gasserian ganglion or more commonly the ophthalmic division of the trigeminal nerve as it passes along the cavernous sinus. The history and neurologic findings are usually sufficient for the diagnosis.

#### NEOPLASIA AS A CAUSE OF FACIAL PAIN

Unfortunately, new growths of the nasopharynx, sinuses, tongue and neck may invade so extensively before their presence is suspected that surgical intervention is not feasible. These tumors, in spite of radium or roentgen ray therapy, frequently cause severe aching pains in the face, which require large doses of opiates for relief. The diagnosis is usually obvious, but occasionally an early case presents difficulties until the nasopharynx is carefully examined. Roentgenograms revealing erosion of the base of the skull or a mass in the sinus are valuable diagnostic aids. Once the diagnosis has been established by biopsy, even if local surgical intervention is contemplated for the relief of pain, nerve section or injection should be considered.

The patient, having been made comfortable, will probably regain his appetite, put on weight and improve his general condition and morale so that a more radical attack may be made upon the tumor. X-ray therapy rarely relieves the pain, in fact in some cases the distress is precipitated or aggravated by such therapy. Too often neurosurgical intervention is thought of as a last resort to be employed only when all else has been tried and found wanting. But the patient, exhausted by his agonies and depressed by the failure of all medical therapies, is so weak in body and spirit that adequate neurosurgical methods are inadvisable. Both Munro<sup>28</sup> and Grant and Weinberger<sup>11</sup> have clearly shown the value of early surgical palliation in malignant disease of the face.

If the pain is confined to the face, alcohol injection of the gasserian ganglion may be sufficient to give relief. However owing to the



invasion of the base of the skull by tumor tissue, such an injection is often difficult and hazardous. For that reason retrogasserian neurectomy should be considered. If this means of relief has been too long delayed and the patient is riddled with metastases in the cervical nodes, a more extensive procedure must be carried out, with section of the trigeminal nerve and the ninth cranial and upper cervical posterior roots on the affected side. This procedure is a formidable one, under such circumstances carrying a fairly high mortality, nevertheless, it is one which is gratifying to the patient. At times this procedure cannot be carried out due to technical difficulties or tumor invasion, in which event mesencephalic tractotomy<sup>28</sup> may give relief, as in the following case.

H. M., a 28 year old accountant, was admitted to the University of Chicago Clinics on April 19, 1944, to the service of Dr. Walter Palmer with the complaint of pain in the left side of the face for one year, inability to open mouth, one year, swelling in the left side of the roof of the mouth, two months, and weight loss of 25 pounds in six months. Five or six years before admission he developed a postnasal drip for which a submucous resection was performed. Some relief was obtained but the discharge continued. In the spring of 1942 he noticed a lump under the left jaw which increased to such a size as to cause difficulty in swallowing. The mass was removed and reported to be Hodgkin's disease.

Early in 1943 a roaring sound was noted in the left ear. At the same time the left jaw began to ache and could not be opened as widely as usual. The pain gradually increased in severity. X-ray therapy (3400 r) was given to the left side of the neck with some temporary relief of the pain. In November 1943 cobra venom was used for the relief of the pain with little success. In December 1943 the patient began to have fever in the afternoon as high as 101° F. associated with general malaise. Since February 1944 he had nosebleeds every week. The pain in the jaw and neck increased. His jaw could be opened only sufficiently to take liquids. The left side of the throat became sore. The pain was so intense that aspirin, codeine and dilantin were used for its relief.

His past history yielded no significant data.

The patient was a well nourished and well developed adult. His thorax, abdomen and extremities presented no abnormalities to clinical examination. There was a 6 cm. scar in the left anterior cervical triangle. The hair was epilated from the left temporal region. The jaw could be opened only 1 to 2 cm., flexion and rotation of the neck were limited although extension was full. A few shotty lymph nodes were palpable in the submaxillary region.

On neurologic examination a small area of hypesthesia was found

anterior and below the left ear Weber's test was localized to the left ear. No other sensory abnormality was found.

On nasopharyngoscopy a rounded mass was seen covering the opening of the left eustachian tube. This mass was biopsied and reported to be carcinoma.

In view of the poor prognosis and relatively little relief from x-ray therapy a retrogasserian neurotomy with section of the ninth cranial and upper cervical roots was suggested. On May 2, 1944, the patient was anesthetized with 100 mg/kg of avertin per rectum. Upon placing him in the cerebellar head rest it was found that his head could be flexed only slightly and that with embarrassment of respiration. For this reason it seemed advisable to abandon the original plan and do a mesencephalic section of the pain fibers for which flexion of the head was unnecessary. A small temporo-occipital bone flap was made, four perforations being used. The bone was fractured at the lateral sinus. The dura mater was incised and a flap turned down. The cerebral veins passing into the lateral sinus were coagulated and cut. The occipital lobe was then elevated exposing the tentorium which was incised to the incisura. The arachnoid over the lateral surfaces of the mesencephalon was gently teased away. The trochlear nerve, superior cerebellar arteries, superior colliculus and lateral sulcus of the mesencephalon were identified. Across the brachium of the inferior colliculus ran two vessels, one of which appeared to be an artery. An incision 5 mm deep was made from the lateral sulcus to just below the superior colliculus, but it was broken at the artery. The occipital lobe was then allowed to fall back into place, the dura mater was closed, the bone flap replaced and the scalp closed with two layers of black silk.

The patient developed a transient hyperthermia to 104° F within ten hours of operation. He suffered no pain in the left side of the face and neck but was quite drowsy. For four days he had periods of irrationality.

Six days after operation the patient was examined in detail. His left pupil was 5 mm, the right 4 mm, but the reactions were brisk. External ocular movements were full. He had a homonymous constriction of the visual fields on the left side. The entire left side of the body was hypalgæsic and the left side of the face and neck analgesic (Fig. 25).

He was discharged on May 13 at which time he walked slowly and unsteadily. His speech was slow and slurred. He still had a left homonymous incomplete hemianopsia. External ocular movements were full. The left pupil was still larger than the right. He was unable to distinguish the head from the point of the pin on the left side of the face and neck. The corneal reflex was active bilaterally. Finger-to-nose test was unsteady terminally on both sides. The extremities were slightly weak but about the same on the two sides. The tendon re-

flexes were active and equal, the plantar reflexes were flexor. Except for the left side of the face and neck, pinprick appeared to be well appreciated over the extremities and body. Below the left knee, hot and cold sensations could not be distinguished.

On May 30 his father wrote "He does not suffer any pain, and his mind is clearing noticeably, but he cannot speak clearly, and the numbness in his left arm and leg still annoys him."



Fig. 25—Photograph of the patient (H. M.) showing the degree of analgesia of the left side of the face ten days after mesencephalic tractotomy for a nasopharyngeal malignancy.

A month later the father wrote that the patient was developing a right hemiparesis and had a large mass on the right side of the neck. It seems obvious that much of his speech difficulties and mental confusion were probably the result of cerebral metastases, present but unrecognized at the time of the operation.

This case illustrates the difficulties in the surgical treatment of intractable facial pain due to neoplasia. In spite of a satisfactory surgical result, the tumor had advanced so far that the full benefits of the operation were not realized. Had operation been done a year

earlier the patient would probably have been spared much suffering by a simpler procedure

#### GENERAL CONSIDERATIONS OF FACIAL PAIN

It has become obvious from this discussion that an accurate description of the facial pain is essential to a clinical diagnosis. Not only the type of pain but its location, modes of initiation and methods of relief are important considerations. A complete physical examination with careful attention to the head is the next desideratum. Although the neurologic examination will frequently elicit no abnormalities, it is important since the absence of sensory and motor disturbance in the face are prerequisite to a diagnosis of certain types of facial pain. Since the sinuses and eyes are frequent causes of facial pain, ophthalmologic and otolaryngologic examinations are essential. Finally, roentgenograms of the skull may confirm a clinical opinion or establish a diagnosis in puzzling cases. Through such a routine examination the basis of many facial pains may be determined. If a psychiatric examination does not elucidate the factors in the remainder, a policy of masterful inactivity while time weaves the tangled threads into a comprehensible pattern, will pay satisfactory dividends both to the patient and physician.

The treatment should be directed towards removal of the causative factors whenever possible. For those cases of *typical trigeminal neuralgia*, retrogasserian neurotomy still remains the best operative treatment. As Grant emphasizes *tic douloureux* does not kill. The treatment must then be as safe and sure as possible. Although operations on the brain stem have distinct theoretical advantages, practically the technical difficulties encountered and the uncertainty of the procedures outweigh the possible gain in the average case. Whether the retrogasserian neurotomy is performed by the subtemporal or suboccipital approach seems to be a matter of the operator's preference and experience. In the hands of most neurosurgeons the subtemporal approach would appear to be the safer of the two.

The surgical treatment of *intractable pain in the face due to malignancy* should be undertaken early so that adequate operative procedures may be performed. If the pain is limited to the face a retrogasserian neurotomy should be sufficient. If the pain extends to the neck a more extensive denervation is necessary. A medullary tractotomy with section of the glossopharyngeal nerve and upper cervical posterior roots would seem to be the simplest method of obtaining relief. Mesencephalic tractotomy may, however, prove to be a less formidable and equally effective procedure.

For those cases of *atypical trigeminal neuralgia*, not relieved by diagnostic novocaine or alcohol block of the Gasserian ganglion, neurectomy is not indicated. Section of the trigeminal nerve in such cases will usually aggravate rather than relieve the condition. If psychiatric therapy is ineffective, psychosurgery may perhaps be tried. Only time can tell what relief, if any, may be expected from prefrontal lobotomy.

## BIBLIOGRAPHY

- 1 Borsook, H, Kremers, M Y and Wiggins, C G The Relief of Symptoms of Major Trigeminal Neuralgia (Tic Douloureux) Following the Use of Vitamin B and Concentrated Liver Extract J A M A, 114 1421-1423, 1940
- 2 Dandy, W E The Brain In Practice of Surgery, edited by D Lewis, 1932, Vol 12, pp 1-682
- 3 Dandy, W E Lesions of Cranial Nerves, Diagnosis and Treatment J Internat. Coll Surgeons, 2 5-13, 1939
- 4 Dandy, W E Results of Removal of Acoustic Tumors by Unilateral Approach Arch Surg, 42 1026-1033, 1941
- 5 Davidoff, L Personal communication
- 6 Frazier, C H, Lewy, F H and Rowe, S N The Origin and Mechanism of Paroxysmal Neuralgic Pain and the Surgical Treatment of Central Pain Brain, 60 44-51, 1937
- 7 Gardner, W J and Babbitt, J A The Occurrence of Tympanic Hemorrhage Following Radical Operation for the Relief of Trigeminal Neuralgia Ann Otol., Rhinol & Laryngol, 38 1040-1045, 1929
- 8 Glaser, M A Atypical Neuralgia, So-called A Critical Analysis of One Hundred and Forty-three Cases Arch Neurol & Psychiat., 20 537-558, 1928
- 9 Grant, F C Results in the Operative Treatment of Major Trigeminal Neuralgia Ann Surg, 107 14-19, 1938
- 10 Grant, F C., Groff, R A and Lewy, F H Section of the Descending Root of the Fifth Cranial Nerve Arch Neurol & Psychiat, 43 498-509, 1940
- 11 Grant, F C and Weinberger, L M Experiences with Intramedullary Tractotomy 1 Relief of Facial Pain and Summary of Operative Results Arch Surg., 42 681-692, 1941
- 12 Grant, F C and Weinberger, L M Experiences with Intramedullary Tractotomy IV Surgery of the Brain Stem and Its Operative Complications Surg, Gynec. & Obst., 72 747-754, 1941
- 13 Hamby, W B Trigeminal Neuralgia Due to Radicular Lesions Arch Surg., 46 555-563, 1943
- 14 Harris, W An Analysis of 1,433 Cases of Paroxysmal Trigeminal Neuralgia (Trigeminal Tic) and the End-Results of Gasserian Alcohol Injection Brain, 63 209-224, 1940
- 15 Horsley, V, Taylor, J and Colman, W S Remarks on the Various Surgical Procedures Devised for the Relief or Cure of Trigeminal Neuralgia (Tic Douloureux) Brit M J., 2 1139-1143, 1191-1193, 1249-1252, 1891
- 16 Horton B T The Use of Histamine in the Treatment of Specific Types of Headache J A M A, 116 377-383, 1941
- 17 Hyndman, O R Tic Douloureux J Internat Coll Surg, 5 192-199, 1942
- 18 Karnosh, L J and Scherb, R F Trophic Lesions in the Distribution of the Trigeminal Nerve J A M A., 115 2144-2148 1940
- 19 Kocher, T Operative Surgery, Vol 9 New York, W Wood & Co, 1894
- 20 Lewy, F H and Frazier, C H The Disturbance of the Time Relation to

Sensitivity in Major Trigeminal Neuralgia A Research Nerv & Ment Dis Proc, 15:497-508 1935

- 21 Love, J G and Woltman H W Trigeminal Neuralgia and Tumors of the Gasserian Ganglia Proc Staff Meet., Mayo Clin., 17:490-496 1942
- 22 Meierowsky A M and Pipito L L Surgical History of Trigeminal Neuralgia Arch. Neurol & Psychiat., 49:574-580, 1943
- 23 Munro D Pain in Cancer of the Face Jaws and Neck An End Result Study of the Relief Afforded by Neurosurgical Methods New England J Med., 224:1049-1053, 1941
- 24 Olivecrona H Tractotomy for Relief of Trigeminal Neuralgia Arch Neurol & Psychiat., 47:544-564 1942
- 25 Rose, A S and Jacobson B M Treatment of Trigeminal Neuralgia with Vitamin B (Thiamine Hydrochloride) Arch Neurol & Psychiat., 44:1307-1311, 1940
- 26 Rose W Abstract of the Lettsomian Lectures on the Surgical Treatment of Trigeminal Neuralgia Brit M J 1:53-55 157-161 261-265, 1892
- 27 Sjöqvist O Studies on Pain Conduction in the Trigeminal Nerve A Contribution to the Surgical Treatment of Facial Pain Acta psychiat et Neurol Suppl. 17:139 pp
- 28 Walker A E. Relief of Pain by Mesencephalic Tractotomy Arch Neurol & Psychiat., 48:861-883 1942
- 29 Weinberger L M and Grant F C Experiences with Intramedullary Tractotomy III Studies in Sensation. Arch Neurol & Psychiat., 48:355 1942
- 30 Weinberger L M and Grant, F C. Experiences with Intramedullary Tractotomy II Immediate and Late Neurologic Complications Arch Neurol & Psychiat., 49:665-682, 1943
- 31 Williams H W A New Angle on Trigeminal Neuralgia. A Study of 245 Cases with Observations on Seasonal Occurrence and Surgical Technique New York State J Med., 41:1177-1180 1941
- 32 Winther K Tractotomy (Sjöqvist) Viewed in the Light of the Pathology of the Medulla Oblongata Acta psychiat et neurol., 14:243-248 1939

## CHORDOTOMY FOR INTRACTABLE PAIN

ADRIEN H. VERBRUGGHEN, M B, CH M, M S \*

INTRACTABLE pain is a problem which has faced the general practitioner for many years and it is likely to continue to do so for a good many more. Scarcely anyone who practices medicine escapes without having had at least a few bitter experiences with patients slowly dying of an incurable disease in which pain is the major problem to which the physician must direct his attention. In many cases the duration of the pain is fortunately short but in others it is long and lingering, and the slow downhill progress of the patient is marked by the most terrifying pain.

Until the beginning of the century the practitioner relied on drugs as a rule to control the pain. The most useful were usually derivatives of morphine. In about 1905 Spiller and Frazier perfected the operation of chordotomy, which simply means the interruption of pain pathways in the spinal cord. Any incision into the cord is called a chordotomy (or cordotomy), but the word is now used to indicate the cutting only of the pain and temperature fibers. When it could be properly applied, in many cases it has been of great help, however, as will be seen as the discussion continues, it has a somewhat limited sphere of usefulness. The procedure is not familiar to the general practitioner nor are its advantages, or recourse would be made to it much more often than it is. It is of value in a variety of conditions such as the gastric crises of tabes, the intractable pain of malignant disease, the intractable pain of amputation stump neuralgia and the intractable pain of phantom limbs. It is for the intractable pain in malignant disease, however, that the operation finds its most frequent application. The anatomy of the part will first be described and later the particular kind of case to which the operation is applicable.

### ANATOMICAL CONSIDERATIONS

The pain fibers of the lower extremities, and for that matter of the trunk and upper extremities also, are gathered together in a bottleneck in the spinothalamic tract. The fibers enter the spinal cord by the posterior roots and cross over to the opposite side, however, they

---

\* Associate Clinical Professor of Neurosurgery (Rush), University of Illinois College of Medicine, Neurosurgeon, Presbyterian, Cook County and Michael Reese Hospitals

may travel up the cord on the same side and cross at various segmental levels up to six segments above the point of entry. To be sure that the pain will cease at any given point it is necessary to cut the spinothalamic tract at least six segments above that intended to be freed from pain. When the pain fiber crosses it does so as a new relay and passes close to the central canal into the spinothalamic tract of the opposite side. The fibers then travel up the spinal cord to the thalamus. (See Fig. 26.)

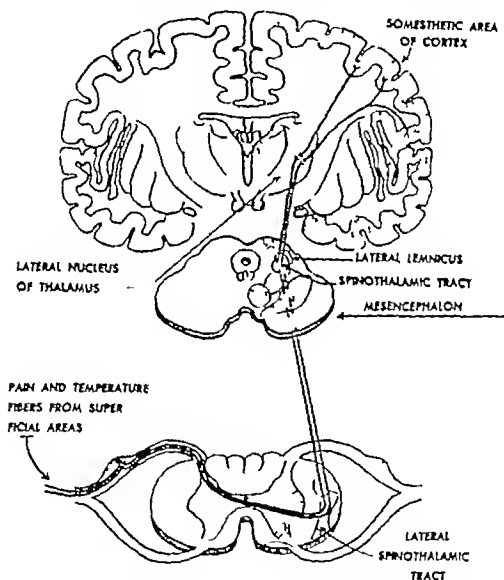


Fig. 26—Simplified diagram of the course of the pain and temperature fibers.

All of the fibers that enter the spinothalamic tract lie deep in the cord at first and later approach the surface. Those that enter the lower tract are more superficially situated than those that enter higher up. So the most superficial incision into the spinothalamic tract would produce anesthesia at the lowest segmental level—that is about the anus and perineum. As the incision is deepened into the spinothalamic tract the leg on the opposite side would become free from pain and temperature sense at a higher and higher level. Finally, if the incision is still further deepened the structures segmentally still closer to the



wound would be deprived of their pain and temperature fibers. In other words, the segmental level of anesthesia is raised by deepening the incision into the spinothalamic tracts. These tracts are situated on the anterolateral aspect of the spinal cord almost immediately anterior to the *dentate ligaments* (Fig. 27). The dentate ligaments are folds of pia mater which support the spinal cord and attach it to the dura mater between the exits of spinal nerves. The dentate ligament is an important landmark in the actual operative procedure. Somewhat pos-

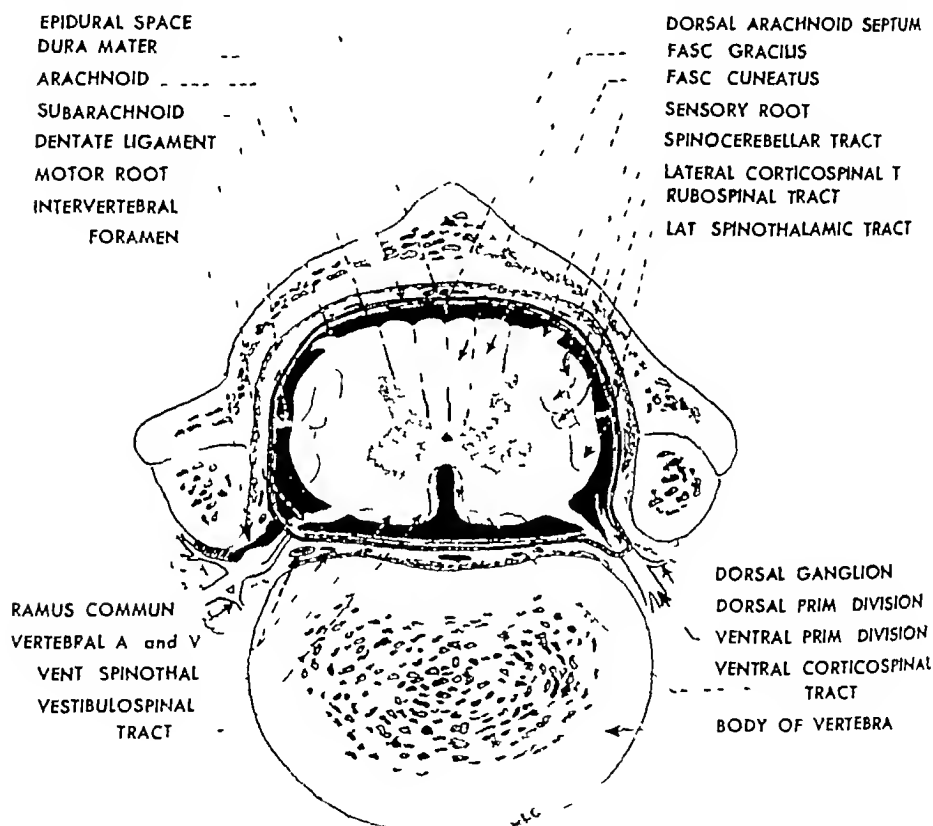


Fig. 27—Transverse section of the spinal cord demonstrating the dentate ligament and the spinothalamic tract

teriorly and at a slightly deeper level run the *pyramidal tracts* and the *rubrospinal tracts*. These two are the main hazards in performing the operation. Naturally, section or even partial section of the pyramidal tracts would result in weakness of the legs, and this is to be avoided. At the same time an insufficiently deep incision into the spinothalamic tract would mean that the level of anesthesia might perhaps not be high enough to include all the painful area.

The incision is actually made about a millimeter anterior to the

dentate ligament and is of a depth of 3 mm into the cord. It is made transversely and the knife is withdrawn at a point corresponding to the line of exit of the anterior nerve roots. If the pain is strictly unilateral, it may be possible to perform a unilateral chordotomy, but as a rule it is necessary to perform chordotomy on both sides.

As a rule chordotomy is performed for intractable pain below the sixth thoracic segments. A high cervical chordotomy around the second cervical segment for patients with intractable pain is high as the

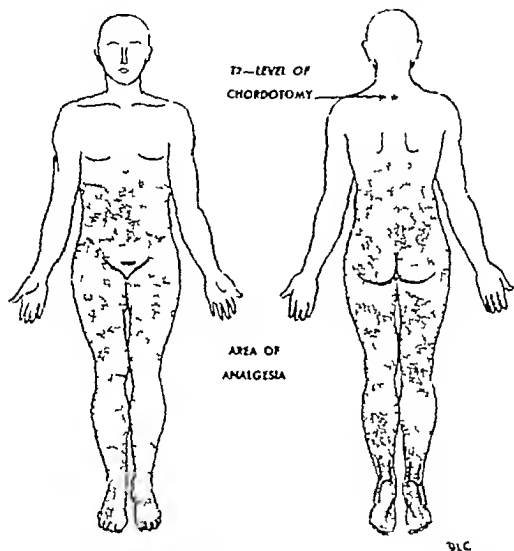


Fig 28.—Extent of analgesia following chordotomy of the second thoracic segment.

shoulder has been reported, but the operative procedure is somewhat more hazardous and the selection of cases much more difficult than for the routine procedure that is being discussed. What is said here has to do only with high thoracic chordotomy, certainly no higher than the first or second thoracic segments. With a properly conducted chordotomy at the second thoracic vertebra it ought to be possible to produce anesthesia up to the xiphoid process with interruption of the pain fibers below that level (Fig 28). This is not quite high enough to relieve all cases with the gastric crises of tabes, but for the

most intractable diseases of the lower abdomen and pelvis, such as carcinoma of the rectum, carcinoma of the prostate, and other similar conditions, the incision is quite high enough

As previously stated, the operation is nearly always bilateral. The patient with an inoperable carcinoma of the uterus may have extremely severe pains down one leg and possibly some minor pains down the other leg. The latter may become much more noticeable after the more severe pain has been relieved. Unilateral chordotomy is only done in a strictly unilateral disease and where the disease is likely to remain unilateral.

#### COMPLICATIONS

It is to be understood, of course, that only pain and temperature fibers are disturbed in this operation, and in such a way as to interfere very little with the rest of the structure of the spinal cord. All the disabilities and dangers and complications of the operation can be foreseen by considering the technic of the operative procedure.

**Retention of Urine**—One of the common disabilities is retention of urine. This is a very sensitive mechanism, especially when there has been interference with the spinal cord. In the days when the chordotomy was done on both sides at the same segmental level and with the two incisions tending to approach one another, there may have been some edema of the cord. This may have led to temporary retention of urine. Some of this can be avoided by staggering the incisions, that is, the incision into the spinothalamic tract is made at a certain level on one side and at a higher or lower level on the other. Even then, however, when incisions are made rather too deep and into the grey matter of the cord, temporary retention of urine may result. As a rule, with suitable care the retention clears up in two or three weeks. The usual procedure is to place an indwelling catheter in the bladder and to give urinary antiseptics. After a week or two the catheter may be clamped off for a few hours to determine whether the patient has any sensation of fullness of the bladder. Under ordinary circumstances, voiding soon becomes normal. In a previously healthy spinal cord and a previously healthy bladder, I have not seen a case of urinary retention and urinary difficulty which continued for more than a month. There may be also some loss of sexual function which, of course, is much more conspicuous in the male. Erection is possible, but orgasm is lost. Orgasm is also lost in the female.

**Weakness of Legs**—An incision which was rather too deep may nick or cause some disturbance of the adjacent pyramidal tracts, and in that case weakness of the legs will develop immediately after operation and may persist two or three weeks and even longer. I have not

seen a case of permanent paraplegia in an otherwise healthy cord, in which the chordotomy was the primary cause of the condition. Most patients on whom a chordotomy is to be performed are usually weak in the first place and their restricted activities are such that some weakness in the legs is not particularly noticeable. Most patients would be willing to sacrifice some strength in their legs to be free from pain for the rest of their lives.

**Mortality Rate**—The mortality rate of the operation is of no practical consideration whatever as most of the individuals for whom the operation is suggested are going to have a very short span of life in any case. The object of this is merely to make that life, such as it is and as long as it lasts, as happy as possible. Simple laminectomy in healthy individuals would give a mortality of less than 1 per cent. If the operation is performed in an otherwise healthy person with, say, an amputation stump neuralgia or the gastric crises of tabes, the mortality rate is extremely low. Exception must be made for morphine addicts. The mortality rate in the person who is dying of malignant disease and has intractable pain may be considerably higher. Furthermore, the question of the mortality rate is really that of the disease for which the chordotomy is performed. The more seriously ill the patient and the more run-down his general condition, the higher is the mortality rate.

#### INDICATIONS FOR AND CONTRAINDICATIONS TO CHORDOTOMY

The *indications* for chordotomy may be said to consist of (1) intractable pain below the costal margin that cannot be successfully controlled by medication and (2) the possibility of the patient's living a few months in a satisfactory general condition.

Naturally, it is important to try to control the pain first by local means and later by general means. If diseased and irritating tissue cannot be removed, general medication must be used, first with non-narcotic drugs and finally with narcotics. It should be estimated that the patient has a few months to live to make the discomfort and the risk of the operation worth his while. It goes without saying that in a very ill debilitated patient, the possibility of doing a major operation, no matter how simple it may be in a healthy person, carries with it a grave risk. Some individuals are at the end of their physical and mental strength and any major procedure could not be contemplated.

The *contraindications* are (1) a short life expectancy, say a month or six weeks, (2) poor general condition, and (3) morphine addiction (possibly). The first two are self-explanatory but the third requires a little discussion. *Morphine addiction* is quite common in those with

intractable pain The use of the word addiction perhaps should be limited to those in whom the taking of morphine, and not the relief of pain, is the primary concern It is very hard to distinguish, on occasion, the one from the other The morphine addict who has gastric crises is very difficult to relieve of pain The desire for the drug prevents the patient from admitting that he has no pain Patients should be offered a chordotomy rather early in a disease which obviously will result in a choice between this and large doses of narcotics If the large doses of narcotics are first used, chordotomy may not be satisfactory In those who have had large doses of morphine before operation, it should not suddenly be withdrawn afterward, as this produces the curious symptoms of restlessness and emotional instability with anorexia which may complicate the picture It is, of course, impossible to treat a patient with intractable pain for very long without giving him morphine, but still it should never be given in large doses, say half a grain every three or four hours for a period of several weeks, before the thought of chordotomy, as an alternative, enters one's mind

#### SELECTION OF CASES

The selection of cases for chordotomy is difficult because pain is such a subjective matter Some people seem to bear pain very well, and in others the slightest pain makes them acutely uncomfortable The practitioner who attends the case usually has a good idea as to how much pain there is and how difficult it is to control However, in selecting patients for chordotomy it is important to know more than this, principally because there are occasionally untoward results which may require explanation These have been mentioned namely, weakness in the legs and retention of urine It is true that these are transitory, but still in patients who have very little pain and who substitute weakness and temporary bladder disturbance for their slight pain, there may be criticism of the management of the case

A useful way of selecting cases is to explain to the patient the type of operation and to magnify the risk involved, for instance, to quote a 10 or 15 per cent risk of life and mention the possibilities of weakness of the legs and transitory bladder disturbance The patient who has a great deal of pain, and to whom that pain is intolerable, does not stop to argue about possible weakness in the legs and possible transitory bladder disturbance, his only concern is immediate relief from the pain Such a patient may say, "Can you operate on me today?" On the other hand, those whose pain is not very severe, judged by this standard, are inclined to ask questions of a rather superficial nature about exactly where the operation is to be per-

formed, the type of incision to be used, the number of laminae to be removed and even if they will be uncomfortable after the operation.

"Will I have to lie in bed for one week or two weeks," and "What about the possible danger of weakness of the legs?" may be asked. I have invariably refused to perform chordotomy on this type of person and, furthermore, I have rarely seen such a patient get into the proper state of mind for a chordotomy later in his illness.

It is always wise to take other members of the family completely into one's confidence. But here again, it is quite possible that some young, robust individual will say that he doesn't wish his mother to be further interfered with and will not allow the operation to be performed, whereas the patient, who may be in perfect control of her senses, is extremely anxious to have it done. When situations such as these arise, it is important to point out to all concerned that this operation is entirely for the relief of pain and will not in any way affect the outcome of the disease. It may be pointed out to the patient that after the operation the amount of morphine can be reduced and that he will be able to live free from pain. The fact that he has a malignant disease is probably not one which should be discussed with him, but with the other members of the family. It is wise to mention this possibility, and to state that in all probability his life will be spent relatively free from pain and with a clear mind.

The process of keeping a patient under morphine for intractable pain for several months is an extremely tedious and tiresome one. The patient is apprehensive for fear some hitch will occur in the administration of the morphine and when he begins to get large doses he lives his life in a perfectly useless mental haze. With the operation an individual might make some use of the time that he has to live, a point which has not been sufficiently emphasized. Certainly there are still plenty of cases in which chordotomy cannot be properly applied and in which the only recourse will be repeated large doses of morphine.

#### TECHNIC

The technic of the operation is quite simple. We will assume that the pain is in the pelvis and is due to a carcinoma of the uterus with perhaps some scar tissue formation from radium treatment, that the pain of the lesion is uncontrollable and that the patient may live another six months. A rectal anesthetic such as avertin is given, if the patient can retain the anesthetic, and she falls asleep in her room. In the operating room an intratracheal tube is passed through which she is given nitrous oxide and oxygen. She is turned over flat on the operating table with her head on a head rest, especially designed for this

purpose, and the skin is marked to perform a laminectomy of the seventh cervical and first and second thoracic laminae. These laminae are removed. The bone is rongeured away more to the right at the lower end of the wound and more to the left at the top. This is done to expose the lateral part of the dura on opposite sides, because we intend to stagger our incisions, and put the right incision in the cord lower down and the left incision higher up. The dura is then opened between ligatures in a dry field and the cord is examined, the dentate ligament is identified, as it holds the cord to the sides of the spinal canal halfway between the exits of spinal nerves. This little dentate ligament is picked up on a mosquito forceps on one side and the cord is rotated so as to make visible its anterolateral surface.

A sharp No. 11 Bard-Parker knife, which is the type of knife with the long point and thin blade, is inserted a millimeter anterior to the dentate ligament and a cut is made forward toward the exit of the anterior root at a depth of not more than 3 millimeters. This depth is a matter of judgment. Some surgeons prefer to use a chordotomy hook which is inserted into the cord and a knife used to cut down upon it. Others use a knife which is guarded so that it cannot well be pushed into the cord for more than 3 millimeters. The procedure described is equally satisfactory. The dentate ligament above the one mentioned is picked up on the opposite side and an incision is made in exactly the same manner as that on the right. There is probably a distance of an inch to an inch and a half, or even two inches, between the two incisions measured in the long axis of the spinal cord. At a later date it will be noticed that the anesthesia is somewhat higher on the side of the higher incision than on the side of the lower incision. The dura is closed and the wound is closed in layers. The whole operation takes perhaps an hour or an hour and a half and it can be relatively bloodless.

**Anesthesia**—Many neurological surgeons feel that an operation of this type ought to be done under local anesthesia so that the segmental level of the anesthesia can be judged. During the operation the patient is tested with a pin and the incisions into the cord are deepened until the zone of anesthesia is well above the level of the pain. This may be very satisfactory in certain types of patients, but those who are really worn out with the pain cannot stand the hustle and bustle of an operative procedure such as this. The local anesthetic has to be very effective or they wear out and begin to cry. In others their condition is such that they do not pay sufficient attention to the examiner who is attempting, while the surgeon is operating, to estimate their level of anesthesia, so that their answers may not be very accurate. More-

over, in order to get it over with, so to speak, they may give definitely incorrect answers, as judged by responses later on when they have recovered from the operative procedure. It is purely a matter of choice and I prefer to operate, for the most part, under general anesthesia. There are certain conditions, however, in which it is wise to have the patients awake in order to estimate the level of the anesthesia before the wound is closed.

**Postoperative Care**—If the patient cannot void, an indwelling catheter is put in place and, of course, from hour to hour he is asked to move his legs, because after an laminectomy, it is possible to have bleeding in the wound and for the patient to lose power in the legs. As the days go on, however, the wound heals, the weakness in the legs is not apparent, at least while in bed, and the patient begins to feel bladder fullness as the catheter is clamped off and, finally, when he is allowed to sit up on the tenth or twelfth day he is able to void. At this point, if the urinary system is clear, the patient is turned over to the general practitioner who sent him, and from then on there is very little difficulty because of the absence of pain. Moreover, if such patients should require local treatment like douches or changing of packs or dressings of other kinds, these may now be done without pain. Before operation the dressings and manipulations may have been extremely painful in fact, so painful that they could not be properly done. From this point on it is possible to clean up local conditions and manipulate the part as much as is necessary to obtain proper local treatment. The patient, free from pain, is able to amuse himself, or perhaps he can work or do things that he finds it necessary to do. For instance, an individual may find it important to make arrangements for his family or to arrange to close his business. As far as the relatives are concerned, it is pleasing to them to be able to see and talk with the patient who otherwise would be merely an object of pity.

#### OTHER PAIN RELIEVING METHODS

There are, of course, other methods of relieving pain, especially in other systems which are not relevant to this discussion. We have not been concerned here with the relief of pain in the arm and breast, nor the relief of pain in the face and jaws. There are neurological surgeons who have performed satisfactory high chordotomies at the second cervical region. For malignant disease of the breast where the arm becomes painful and edematous some of these have been entirely satisfactory, others have not been so satisfactory and the mortality rate is sometimes unexpectedly high because death from respiratory failure is not uncommon. The pain in the arms and chest from malig-



nant disease of the breast is perhaps better controlled by posterior root section. Satisfactory results have been reported following this procedure. Pain in the face, mouth and jaws from carcinoma may be relieved by section of the sensory root of the fifth nerve, section of the ninth nerve or by an intramedullary tractotomy. Under certain circumstances these procedures may be combined and section of the sensory roots of the upper cervical nerves may be added to them. We of course have not discussed the pain of visceral disease such as the pain of interstitial cystitis or Hunner's ulcer. We have not discussed the pain of dysmenorrhea or angina pectoris, nor have we discussed causalgic pain. These belong in the class of sympathetic nerve pains which are usually relieved by direct attack on the sympathetic system. Chordotomies have to be at a considerable distance above the site of visceral pain in order to be satisfactory.

#### ILLUSTRATIVE CASES

CASE I—Mr. G. K., 39 years old, was admitted to the Presbyterian Hospital Chicago in October 1939, complaining of constant knife-like pain in the perineum. In February 1939 a bladder tumor, as well as his left kidney, had been removed. In August 1939 a further operation was performed on the bladder tumor. The tumors were said to be papillomas. The pain in the perineum had been present for a month before the second operation. In September 1939 the patient was having severe pain in the perineum but, as his bowels did not move properly, and because of the pain, his abdomen was opened and adhesions between the bowel and the bladder were reported to have been removed. The pain in the perineum was not abated. An epidural injection did not relieve him.

On October 14 an epidural injection of novocaine was given by me with instant relief. A few days later, with the patient in a suitable position, 1 cc. of absolute alcohol was injected between the fourth and fifth lumbar vertebrae. This was done very slowly. At first there was a burning sensation in the perineum, which disappeared in about one-half hour. (The pain disappeared with the injection.) The patient immediately had more trouble in emptying his bladder than he had before the injection. Next day an indwelling catheter was inserted. Six weeks after the injection, he was beginning to void without a catheter. Three months later he returned and the pain had reappeared in the perineum. He felt that the pain was so severe in this case that a chordotomy should be done.

A chordotomy was performed according to the routine procedure described in this paper and the patient remained free from pain until his death some five months later. For the first few days there was weakness in the legs and as soon as the operation was done it was

necessary to replace a catheter in the bladder. In this case it was possible to treat the patient before he had begun to rely too much on morphine and while he was in good condition. However, his bladder tumor finally caused his death at a later date but at least he spent the intervening five months in fairly good condition.

CASE II—A very similar case was that of another man, 52 years of age, with an inoperable malignancy of the prostate causing intractable pain. In every other way he seemed fairly normal. He walked into the hospital for relief of his pain, and readily submitted to bilateral chordotomy which was performed in 1932. Following the operation his legs were weak for a few days and his bladder gave him trouble and he had to have an indwelling catheter. In a month his legs had almost regained their normal power and he had little trouble with his bladder from that time until his death fourteen months later. He was extremely satisfied with the operative procedure.

CASE III—Mrs. D. B., 79 years of age, was seen by me in consultation with a practitioner in a neighboring hospital. For the last three months she had had a rapidly developing paraplegia from a carcinoma of the pelvis with metastases to the lumbar spine. She was having agonizing pain in the legs and in the lower abdomen. This pain would come on in spasms and caused the patient to break out in a cold sweat. She was extremely apprehensive of the next attack of pain and spent most of her time in the act of prayer. Although the condition of this patient seemed far from satisfactory, the acuteness of the pain was such that morphine was of little or no value to her. In spite of her age, a chordotomy was done with immediate relief of pain until her death six weeks later. Except for the extraordinary severity of the pain one would not perform an operation of this magnitude in a patient in this condition. However, for the six weeks after the operation she was able to converse with her grandchildren and other relatives and all in all these six weeks made the procedure seem worth while.

CASE IV—J. W., 49 years of age, first came to Cook County Hospital on January 10, 1940, with amputation stump neuralgia. He had had the right leg amputated below the knee as the result of an injury in 1931. In 1933 he had a reamputation with a short stump. Pain radiated down the back of the stump and he had had numerous injections and x-ray treatments. On January 17 the sciatic nerve was exposed and cut back about two inches from the scar without any further treatment. On April 8, 1940, he came in complaining of pain down the side of the leg and he stated that the pain down the back of the leg was not conspicuous at this time. In other words, the section of the sciatic nerve had relieved some pain. The lateral cutaneous nerve of

the thigh seemed to be involved on this occasion and was cut. On November 13, 1940, he was still having intractable pains rather unlocalized in his right leg and at this time it was suggested that a chordotomy be done. Chordotomy was done on November 20, 1940, on one side only with relief of pain. Apparently the relief has been maintained because the patient has been seen as late as January 1944 complaining of other things but not the amputation stump neuralgia. All amputation stump neuralgias do not respond to chordotomy. It has been suggested lately that possibly the way to deal with some of these is to ablate the sensory cortex corresponding to the leg.

CASE V—Mr M W, 60 years of age, was first seen at Cook County Hospital on February 21, 1939. He was complaining of acute abdominal pain radiating around both sides of the epigastrium. This had been present since 1932. In 1916 he had contracted syphilis and had been treated for it. Occasionally he vomited with pain, both pupils reacted fairly well to light and somewhat to accommodation. The ankle jerks and knee jerks were very feeble in both legs. The Wassermann reaction was negative on December 12, 1939. The history, especially that of the pain, made it certain that this was an example of the gastric crises of tabes and on January 10, 1940, a chordotomy was done. He was seen for several months, and one month after operation he stated that the sharp shooting pains had stopped, but he did have a dull ache. For some unknown reason he bled copiously from the bowel on two occasions. By May, five months later, he reported finally that he felt very much better and had only occasional slight twinges of pain above the zone of anesthesia produced by the chordotomy. On account of the lessening of the pain he was able to return to work and become a useful citizen and economically self supporting.

#### COMMENT

One may say in summary that this procedure is one which is too infrequently employed, partly because of lack of appreciation of the indications and the benefits to be derived, and partly because of reluctance to initiate new treatment or upset an established routine. The patient who has a diagnosis of incurable disease with intractable pain would have to be moved perhaps from a distance to a hospital where a neurological surgeon could perform the operation, and then he must be moved back. All of these things are drawbacks to taking the step toward chordotomy. In the majority of cases, however, where the operation is well thought out and properly indicated the result is very satisfactory, not only to the attending physician but to the relatives and especially to the patient.

## PROTRUSION OF THE INTERVERTEBRAL DISK

HAROLD C. VORIS, M.D.\*

PROTRUSION or herniation of the intervertebral disk has been known as a pathologic entity for a half century. Although its clinical significance escaped surgeons and neurologists for most of that period, the last ten years have seen an intense interest in the subject. Operation has been done in a large number of cases (Love and Walsh), and many articles and even monographs have appeared on the subject. It is now apparent that this lesion is much more frequent than was at first suspected, that it can often be recognized by careful clinical history and examination and that in properly selected cases surgical removal is the treatment of choice. These herniations may occur at any level of the spine but they predominate in the lumbar region and the great majority are from the fourth and fifth lumbar intervertebral disks. Recurrent pain of the so called root type is the usual complaint, only rarely does the patient present gross neurologic defects. Protrusions from disks above the first lumbar are the most apt to cause such gross neurologic defects by pressure on the spinal cord, simulating cord tumor. Even at these higher levels it has recently been recognized (Semmes and Murphy) that a small, lateral protrusion of the intervertebral disk may cause a syndrome of root pain with minimal objective neurologic findings comparable to the classic syndrome at the lumbar level.

Since over 90 per cent of disk protrusions are from the lumbar disks, and most of these from the fourth and fifth lumbar disks, this clinic will be confined to the problems arising in this group. Five cases illustrating certain important points will be presented in some detail with discussion of the individual problems of each case. Then a general discussion of various phases of diagnosis, treatment and results will complete the presentation.

CASE I—M D K, a physician 30 years of age, was referred by his brother, also a physician. Five years before while serving an internship he had had an attack of "lumbago" for two weeks. He recovered completely from this for fifteen months and then recurrence took place.

---

From Loyola University Medical School and Mercy Hospital Loyola University Clinics.

\*Clinical Professor of Surgery (Neurological) Loyola University Medical School Senior Surgeon (Neurological) Mercy Hospital

in the shape of mild "nagging" pain in the lower part of the back. This persisted with remissions and exacerbations. A sacroiliac belt had been of slight help. Treatment with an autogenous vaccine cultured from the nasopharynx had given considerable relief on another occasion. The patient suffered from chronic sinusitis and had noted a definite relationship between "flare-ups" of his sinus trouble and exacerbations of his low back pain. Both he and his brother had consequently considered his low back pain to be the result of absorption of toxins from his chronic sinusitis.

One month previously the patient had, for the first time, radiation of pain into the posterior aspect of the right thigh and leg. This pain was worse on coughing, sneezing or straining at stool. No history of definite injury was obtained, but the patient had always been robust and had done considerable heavy work at certain periods of his life.

General physical examination was essentially negative. Neurologic examination revealed diminution of the right ankle jerk and hypesthesia to pinprick on the lateral border of the right foot. The circumference of the right calf was 36 cm, the left 37 cm, the patient was right handed. An air myelogram was performed on March 9, 1940. With the head lowered to an angle of 35 degrees on the tilting table a spinal puncture was performed at the first lumbar interspace and 35 cc of spinal fluid were removed and air substituted. The total protein content of this fluid was elevated to 78 mg. Lateral and anteroposterior stereoscopic films revealed a defect in the right side of the air column opposite the lumbosacral interspace.

Operation on March 12, 1940 consisted of a right partial hemilaminectomy of the adjacent portions of the spines and laminae of the fifth lumbar and first sacral vertebrae. This together with resection of the ligamentum flavum exposed an area of dura about 2 by 1.5 cm. Retraction of the right fifth lumbar root exposed a large protrusion of the disk which had not ruptured completely through the posterior longitudinal spinal ligament. A cruciate incision was made in this structure and the fragments of disk material extruded and were readily removed. An unusual amount of fragmented cartilage was removed and a cavity 2 cm deep in the disk was produced. The dura was not opened and the wound was closed. Convalescence was uneventful and the patient left the hospital on March 29, 1940.

The patient returned to his office three weeks later but was cautioned against lifting or straining for a period of three months. Three months later he considered himself perfectly well. The right ankle jerk was still diminished and straight leg raising on the right still gave slight discomfort. The patient has remained well since, carrying on his practice without interruption. Recently he received a commission in the Medical Corps of the Army of the United States and has been ordered to active duty.

*Comment*—This case can be considered typical of the syndrome of unilateral protrusion of the fourth or fifth lumbar disk. After a considerable period of recurrent low back pain, unilateral sciatic radiation appeared. The sciatic pain was exacerbated by coughing, sneezing or straining. The ankle jerk was diminished on the affected side and there was definite hypesthesia about the foot on that side. Spinal fluid showed a mild increase in the total protein, and a contrast myelogram showed a definite filling defect of the spinal canal. Operative removal of the protrusion gave an entirely satisfactory result.

The exacerbation of the patient's low back pain with recurrence of his chronic sinus infection is of great interest. It shows that the presence of a known focus of infection and even a demonstrable clinical relationship between the focus of infection and the nerve pain in question does not prove the pain to be purely inflammatory or toxic. In this instance the irritated nerve root must have been a *locus minoris resistentiae* for toxins from the infected sinuses. A considerable number of patients have low back pain for months or years before the onset of nerve root pain. Roope has described the innervation of the annulus fibrosus and the posterior longitudinal ligament. In the early stages of disk protrusion this innervation is responsible for the patient's pain. Only when the protrusion is large enough or far enough laterally to impinge on the nerve root will the patient have radiating pain. Both the nerve root and the protrusion of the disk are slightly affected by postural changes and by muscle spasm. This accounts for the frequent exacerbations, often initiated by muscular strains, and the remissions afforded by bed rest, heat, diathermy and so forth. Many patients who are able and willing to limit their physical activity can avoid serious recurrences and live satisfactorily with their disk protrusion.

Spinal fluid examination and contrast myelography are not essential in the diagnosis of typical cases and were not here. The total protein content of the spinal fluid is often not elevated, and this finding while of great help when positive has no negative value. Contrast myelograms were thought at one time to be necessary in all cases. In fact it is doubtful if the intervertebral disk syndrome would have become well recognized without the aid of contrast myelography. Air and oxygen are the least desirable of the mediums in general use from a roentgenographic standpoint, but both have the advantage of rapid and complete absorption, leaving no trace of their presence and both produce little or no irritation. Lipiodol is far superior from a roentgenographic standpoint but is difficult to remove except at operation. In the writer's experience no irritative effects from lipiodol are

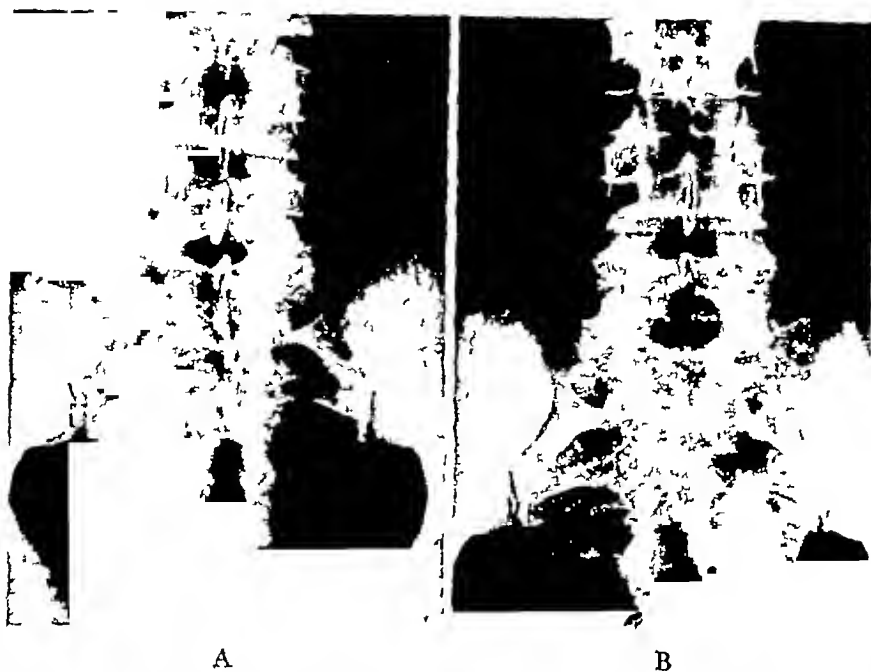


Fig 29 (Case I) —A, Preoperative roentgenogram, anteroposterior view B, Postoperative roentgenogram, anteroposterior view Note small amount of bone removal

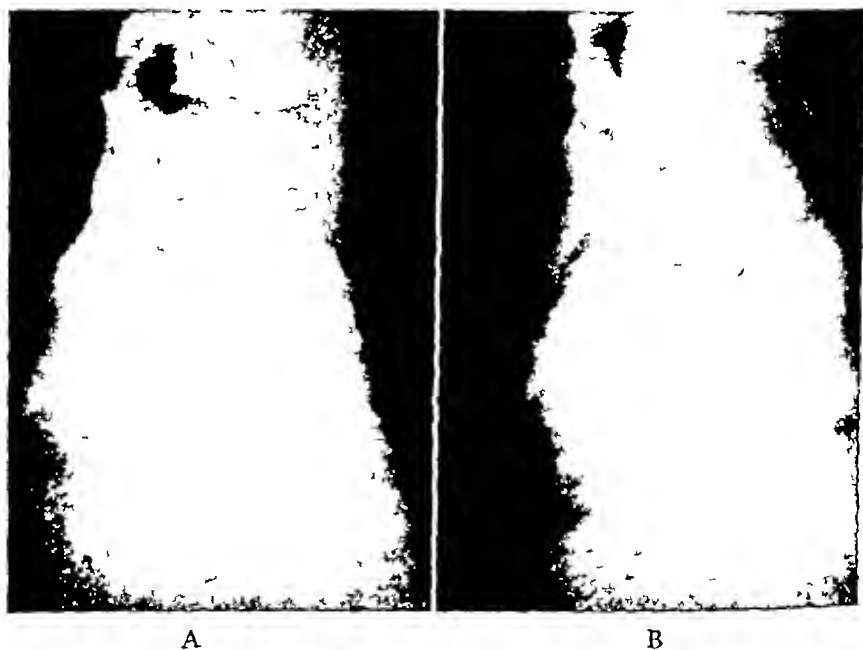


Fig 30 (Case I) —A Preoperative roentgenogram, lateral view B, Postoperative (six months) roentgenogram, lateral view There is no change in the lumbo-sacral disk space which was narrowed before operation

clinically as a rule, rarely such effects are definitely produced. The new substance, pantopaque, is comparable to lipiodol from a roentgenographic standpoint and has the advantage of being readily removable by aspiration through a spinal needle. It is now becoming generally available.

This patient has had a good operative result over a four year period. The operative procedure consisted of simple removal of the protruded and fragmented portion of the disk through a limited but adequate operative exposure. As Fig. 29 shows bone removal was minimal. Although a large cavity was produced in the fifth lumbar disk, a lateral roentgenogram six months later compared with a preoperative roentgenogram (Fig. 30) showed no decrease in the intervertebral space. Spinal fusion was not done in this case although one of the so-called indications was present—that of low back pain for several years before the onset of sciatic pain.

CASE II—M. C., a punch press operator 45 years of age, had suffered from recurrent low back pain for the past twelve years. He had been treated more or less continuously as a case of spinal arthritis. Two weeks before admission he had begun to have pain radiating into the left lower extremity but was able to continue work until five days later when on arising in the morning he was paralyzed from the knees down. Since that time urinary retention and fecal incontinence had been present and the patient had been bedridden.

Neurological examination revealed weakness of the thigh muscles with paralysis of the calf and peroneal muscles. The right knee jerk was active, the left absent and both ankle jerks absent. Cutaneous sensation was lost over the posterior aspects of the buttocks and thighs (third to fifth sacral dermatomes) and impaired on the posterior aspects of the legs, over the feet and the anterior aspect of the lower third of both legs (fourth lumbar to second sacral dermatomes). There was an area of hyperesthesia to pinprick on the dorsum of each foot. Vibration sense was moderately impaired at the left ankle and slightly at the right. Position sense was impaired in the left toes.

A neurological consultant had performed a spinal puncture and injected lipiodol. He had not obtained fluid at the third or fourth lumbar interspaces but had obtained xanthochromic fluid that coagulated on standing at the fifth lumbar interspace. No rise in spinal manometric pressure had been noted on bilateral jugular compression. X-rays taken after his injection of lipiodol at that level showed all of the lipiodol below the lower part of the body of the fourth lumbar vertebra.

The preoperative diagnosis was tumor of the cauda equina opposite the third and fourth lumbar vertebrae. Operation was performed March 26, 1940 and consisted of laminectomy of the spines and laminae of the third, fourth and fifth lumbar vertebrae. When the lamina



of the fourth lumbar vertebra was removed on the left side, a tightly rolled extradural mass extruded itself and spontaneously unrolled. It proved to be a ragged piece of fibrocartilage 4 by 2.5 by 0.7 cm (Fig 31). Its inferior and anterior corner was still attached to the intervertebral disk between the fourth and fifth lumbar vertebra. It was readily removed. The ragged cavity in the intervertebral disk proved to contain no loose or fragmented cartilage. The dura was opened and the previously injected lipiodol was removed. The nerve roots were swollen and markedly injected.

Convalescence was uneventful. At the patient's dismissal from the hospital three weeks later bladder function had satisfactorily returned but the neurologic status was otherwise unchanged. Nine months later he was walking well with only moderately diminished strength and

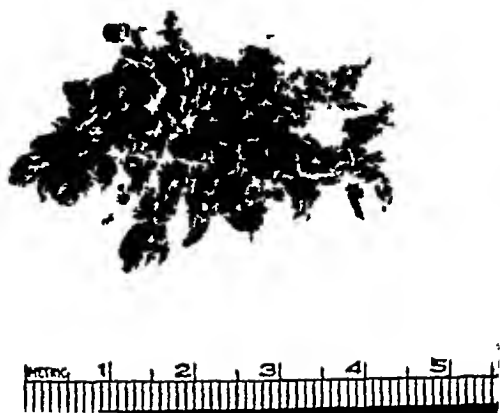


Fig 31 (Case II) —Photograph of extruded portion of disk removed at operation

tone in the calf muscles. The left patellar reflex was diminished. Both ankle jerks were present but diminished. Sensation was still impaired in the third to fifth sacral dermatomes bilaterally. The patient claimed no difficulty with bladder function but admitted some difficulty in controlling the rectal sphincter. Four years later he reported good control of bladder and bowels, residual atrophy of the calf muscles, and complained only of easy fatigue in his lower extremities. He estimated his percentage of recovery at 90 per cent.

*Comment*—This was an extraordinary case. After years of low back pain, sudden and complete loss of neurologic function below the fourth lumbar roots developed, preceded by root pain of only a few days' duration. In the absence of a definite injury or strain it is diffi-

cult to explain the massive extrusion of the ruptured cartilage. Since then I have had a similar case. A 45 year old priest had had low back pain for ten years with recurrent sciatic radiation for a year. While in the hospital receiving conservative treatment he coughed at stool one morning and was seized with excruciating low back and bilateral loss of function below the third lumbar segment. A preoperative diagnosis of massive extrusion of intervertebral disk cartilage was made and verified at operation. The operative findings were similar to those of Case II except that the extrusion was one segment higher. A similar case was reported by Middleton and Teacher in 1911, and two others by Dandy in 1929. Recently French and Payne have reported eight cases of compression of the cauda equina due to disk protrusions. Such cases as this are rare but should be thought of in the event of sudden paraplegia, especially if the onset is associated with muscular strain or wrenching. If the extrusion is below the first lumbar disk the prognosis for recovery is good, especially with early operation. Such an accident above the first lumbar disk will usually result in permanent damage to the spinal cord. Localization is obvious from the neurologic findings, spinal puncture confirms the presence of a subarachnoid block, contrast myelography should not be necessary.

CASE III—M. N., a 40 year old mason, had injured himself in a fall twenty years before when he landed on his buttocks. Recurrent, low back pain had plagued him since and for the past four years there had been recurrent left sciatic radiation of the pain. This was exacerbated by coughing or sneezing and when sitting for any length of time numbness and tingling of the left lower extremity was noted. About a month before, right sciatic pain had appeared but was not as severe as on the left nor were there any paresthesias on the right side.

Examination revealed a markedly positive Lasègue (straight leg raising) sign on the left and a mildly positive one on the right. There was tenderness to palpation at the lumbosacral junction. Both ankle jerks were absent and there was hypesthesia to pinprick on the border of both feet. An air myelogram was carried out, 20 cc of spinal fluid being removed and air substituted. The total protein content of the fluid was 58 mg. The myelograms were not satisfactory. No air was seen below the fourth lumbar interspace.

Operation on September 22, 1942 consisted of partial laminectomy of the spines and laminae of the fourth and fifth lumbar and the first sacral vertebrae. The ligamentum flavum was resected at both the fourth and fifth lumbar interspaces. Part of the lamina of the fifth lumbar vertebra, a ridge of bone 15 mm wide, was preserved. The fifth lumbar and first sacral roots were markedly swollen but no evidence of disk protrusion at the lumbosacral level was found. At the

level of the fourth interspace there was a small protrusion on the left side near the midline. There was no rupture of the posterior longitudinal ligament. When the protrusion was incised, very little fragmented disk material escaped or could be removed. However, there was an extensive degeneration of the intervertebral disk as there was a cavity about 2 cm deep in the disk into which the aspirator tip or curet could be readily introduced. The dura was not opened and the wound was closed.

The immediate convalescence was uneventful and the patient was dismissed from the hospital on October 8, 1942. He was next seen on October 22, 1942 complaining of "a catch in his back" and bilateral radiation of pain into both thighs anteriorly. There was a marked list of the lumbar spine to the right and straight leg raising was painful, especially on the left. He was readmitted to the hospital and improved rapidly with inductotherm treatments, being dismissed again four days later. However, he continued to complain of low back pain and has not been able to work steadily. Spinal fusion has been advised but the patient has refused further surgery.

*Comment*—This case is an example of an unsatisfactory result. Spinal fusion was certainly indicated in this case and should have been done at the operation for removal of the disk protrusion. The evidence at operation of extensive disk degeneration without any marked protrusion suggests that the protrusion was of relatively little importance and the pathologic change within the disk of chief importance. This patient's attitude and personality made him a poor choice for surgical treatment. He was pessimistic before operation about the likelihood of relief and he had a low pain threshold with a tendency to exaggerate his complaints. For many years he had complained of a "weak stomach" with frequent gastric upsets, although repeated examinations by capable gastroenterologists had never revealed any organic cause for these disturbances. We would have done well not to have advised operation on this patient, if operated on he should have had a spinal fusion combined with removal of the disk protrusion.

CASE IV—J. N., a 35 year old grain broker, had had recurrent, low back pain for eight years, usually brought on by exercise and more frequent in the winter months. Extensive and prolonged orthopedic treatment had failed to give relief. For a week the pain had radiated down the posterior aspect of the right lower extremity and had been exacerbated by coughing or sneezing. The patient had been an active athlete in high school and college and had done heavy work during school vacations. He could not, however, give a history of a specific back strain or injury.

Examination revealed a moderately positive right Lasegue sign and definite lumbosacral tenderness. The right ankle jerk was diminished, there were no sensory changes. An air myelogram was carried out, 30 cc of spinal fluid being removed and air substituted. The total protein content of the spinal fluid was 67 mg. The myelograms showed a defect in the air column on the right at the fourth lumbar interspace.

Because of the minimal objective neurologic findings and the long history of low back pain, and with the case of M. N. in mind, further orthopedic consultation was advised. Dr. Perry Rogers saw the patient, concurred in the diagnosis of protrusion of an intervertebral disk and advised the combination of spinal fusion with removal of the

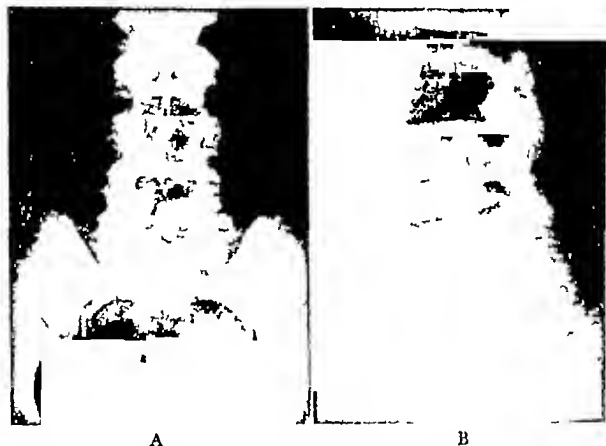


Fig. 37 (Case IV) —A Postoperative roentgenogram, anteroposterior view, six weeks after combined operation. B, Lateral view.

disk protrusion. The preoperative diagnosis was protrusion of the fourth intervertebral disk on the right.

Operation on February 2, 1943 consisted of exposure of the spines and laminae from the fourth lumbar to the second sacral vertebrae. The ligamentum flavum was widely resected at the fourth and fifth lumbar interspaces and a small portion of the adjacent laminae nibbled away. There was no evidence of disk protrusion at the fourth lumbar interspace. On the right, near the midline at the lumbosacral interspace, there was a large protrusion. The posterior longitudinal ligament was not ruptured but was so thin over the protrusion that it ruptured on gentle probing. A large amount of fragmented disk material was removed. The cavity in the disk after removal of the

fragmented material was 3 cm deep. Dr. Rogers then performed a Hibbs' type spinal fusion, using plaques of bone from the outer table of the right ilium, in addition to slabs of bone from the spinous processes, the laminae, and the posterior aspect of the sacrum.

Convalescence was uneventful. The patient was ambulatory in a body cast at the time of his dismissal on February 24, 1943. The cast was removed six weeks after operation. Figure 32 shows roentgenograms taken at that time. During the summer of 1943 he played tennis without ill effects. When last seen in May of 1944 he was perfectly well and was enjoying golf, badminton and tennis.

*Comment*—The result in this case is in marked contrast to that obtained in Case III with a comparable history. However, it would not be accurate to carry the comparison further. This patient was a much more stable individual—a very intelligent and highly successful business man who cooperated fully in his treatment. Moreover, he had a large protrusion of the disk which adequately accounted for his root pain. However, the very satisfactory result speaks well for the combined operation. It should be noted that the air myelogram not only failed to localize the lesion but was actually misleading, indicating a nonexistent protrusion at the fourth lumbar disk. Even at best air myelography is far inferior from a roentgenographic standpoint to lipiodol or pantopaque.

CASE V—D. M., a 27 year old housewife, had strained her back nine months before while carrying her baby upstairs in its carriage. Low back pain followed and within a few days became severe, and right sciatic radiation was noted with numbness of the right buttock and posterior aspect of the right thigh. The numbness had gradually improved but still persisted in considerable degree. She had been delivered of another child six months later but did not feel that her labor pains had been different from former labors or that labor had affected her low back or sciatic pain. The pain had been recurrent with every effort to resume normal activity.

Examination revealed a moderately positive Lasègue sign on the right and absence of the right ankle jerk. There was marked hypesthesia to pinprick in the right side of the perineum and the posterior aspect of the right thigh (third to fifth sacral dermatomes). An air myelogram was done, 40 cc of fluid were removed and air substituted. The total protein content of the spinal fluid was 50 mg per 100 cc. The myelograms showed a shift of the air column to the left opposite the fifth lumbar interspace. A diagnosis was made of a large disk protrusion on the right at the lumbosacral level. Neoplasm was considered a possibility because of the involvement of sacral dermatomes.

Operation on January 8, 1944 was a right hemilaminectomy of the fifth lumbar vertebra. Initially the ligamentum flavum was resected on the right at the fourth and fifth lumbar interspaces and the resultant opening then enlarged by nibbling away the adjacent laminae slightly with rongeurs. With this exposure no disk protrusion could be seen, but after complete removal of the right side of the lamina of the fifth lumbar vertebra a protrusion of the lumbosacral disk could be visualized near the midline projecting upward so that it could not be seen through the interlaminar space. The posterior longitudinal ligament was not ruptured, after its incision a considerable amount of fragmented cartilage and nucleus pulposus was removed. Extradural bleeding was troublesome and finally required several muscle pledgets to control.

Convalescence was uneventful and the patient left the hospital on January 24, 1944. The sensation in the right perineum, buttock and posterior thigh had improved, especially over the perineum and buttock. A month later no objective sensory disturbance could be found although subjective numbness of the posterior aspect of the right thigh was still present. The patient has not been seen since but reports by letter that she is entirely well.

*Comment*—This patient's sciatic radiation began within a few days of her low back pain. The onset was related to a definite back strain. Unusual features were the early paresthesias in the sacral dermatomes and the objective sensory disturbances in these dermatomes on examination. This protrusion near the midline was apparently large from the onset so that sciatic radiation of pain and sensory disturbances appeared very early. Some improvement had followed conservative treatment but she had been practically incapacitated from the time of her injury. She was six months' pregnant at the time of the onset but what role that played in the severity and persistence of her symptoms is difficult to assess. She noted no improvement after delivery. At operation this patient's disk protrusion could not be visualized through the usual interlaminar approach and complete hemilaminectomy of the fifth lumbar vertebra was necessary. Neurologic surgeons know that laminectomy, even if extensive, is not disabling nor does it weaken the spine if the articular facets are preserved. Other things being equal it is of course desirable to remove as little tissue and destroy normal relationships as little as possible in the removal of a disk protrusion. This desire should not lead to the failure to visualize the protrusions or adequately remove them through lack of exposure. The surgeon should not operate unless he is convinced that a disk protrusion is present, if he does operate, while his initial exposure may be limited

he should never fail to make an exposure adequate to visualize and remove the obstruction

#### GENERAL COMMENT

**The History**—The importance of a good history cannot be overestimated. Root pain, whether in the sciatic radiation or elsewhere, has certain rather constant characteristics. When present its location is constant, it is often worse at night, and it is usually exacerbated by coughing, sneezing or muscular straining. The past history must be carefully inquired into for attacks of back pain or sciatica in the past and for back injury or strain.

**Examination**—On examination the patient may limp on the affected side if the pain is severe. Often the lumbar spine lists away from the affected side, occasionally to that side. Localized tenderness at the affected interspace is a frequent finding. Straight leg raising is almost always painful, sometimes extremely so. The absence or impairment of the ankle jerk on the affected side or some degree of sensory disturbance in the affected dermatome or dermatomes is exceedingly important. In my own experience such objective neurologic findings were absent in only 15 per cent of the cases in which a disk protrusion was found at operation. On the other hand, in the cases in which I failed to find a disk protrusion, such objective neurologic findings were never present. It is obvious from this that, in the absence of objective neurologic findings, great care should be exercised in making a diagnosis of protruded disk. Probably contrast myelography should be used in all of these cases. It must be emphasized that the objective neurologic findings referred to are minimal and must be sought for carefully and skillfully. Bradford and Spurling, and Semmes have well emphasized the importance of careful neurologic examination.

**Selection of Patients for Operation**—The selection of patients for operation is very important. As has already been stated, many patients with mild symptoms can live fairly comfortably with their disk protrusion if they are brought through an occasional exacerbation of their symptoms by conservative treatment. This is particularly true of those individuals who are fortunate enough to be able and willing to avoid hard physical labor or strenuous exercise. Many patients with acute back strain have injury to the intervertebral disk and the annulus fibrosus or posterior longitudinal spinal ligament. However, with rest and perhaps temporary immobilization healing takes place and there is no recurrence of symptoms. Perhaps an improvement in the early management of low back injuries might lessen the incidence of later disk protrusions. In addition to those patients whose symptoms are not sufficiently marked to warrant surgical intervention, there is a group

of patients who do have severe and disabling complaints. However, these individuals, because of their personality and attitude (Case III) are likely to continue to complain after an apparently successful operative procedure or they may develop a new set of complaints after operation. All surgeons know this type of patient and learn to avoid elective operative procedures on him whenever possible.

Another group of patients with disk protrusions that is notoriously apt to obtain poor results from surgery consists of the compensation cases. Where it is feasible, the patient with a compensation problem should be encouraged to obtain a final settlement of his case and then seek relief from surgery. Such settlement should of course take into account his prospective medical and hospital expense. When surgery is carried out while the patient is still receiving compensation, the patient should be told frankly that after operation he will be expected gradually to resume full activity and finally return to work even at the expense of minor discomfort. Patients in this group with low pain thresholds, inadequate personalities, or who indicate resentment against their employer or the insurance carrier will seldom obtain a good result, at least during the period of compensation. The patient who has legal proceedings pending, either in court or before the Industrial Board, will seldom cease to complain until after these proceedings have been settled.

Patients who do require operation fall into three main groups. Those in the first group have relatively mild symptoms but circumstances or the patient's own desires (Case IV) demand considerable physical activity and the persistent recurrence of symptoms finally brings them to operation. If they can change their occupation or if they will give up strenuous exercise, an operation may be avoided. Many cannot do the former, some refuse the latter alternative. Selection of cases must be carried out carefully in this group.

A second group in spite of conservative treatment and limitation of activity continues to have recurrence of pain and also finally comes to operation (Case I). Patients in this group present fewer problems than the first group. Trial of conservative treatment has been adequate and the patient has been cooperative. The persistence of recurrences under such conditions warrants surgical intervention.

Finally there is a group of patients whose pain is constant and severe with any activity (Case V) or who develop marked objective neurologic disability (Case II). These patients present an absolute indication for operation because of their disability and suffering. Once the diagnosis is established, and in this group that is usually not difficult, surgery is indicated.



**Surgical Management**—The surgical removal of a disk protrusion, especially through a limited exposure, requires an accurate anatomical knowledge of the region involved plus certain special instruments and technic. The management of epidural bleeding is often troublesome, interfering with the exposure and removal of the lesion. If it is not controlled before the closure of the wound, postoperative hematoma with serious neurologic sequelae may occur. The use of suction and electrocoagulation is of great help. Small implants of muscle or, as recently suggested by Ingraham, Bailey and Nulsen, of pieces of fibrin foam soaked in thrombin may be necessary. Small cottonoid strips, cotton pledgets, special nerve root retractors, special rongeurs and biopsy punches are all of great assistance and represent part of the regular armamentarium of the neurologic surgeon.

The most debated question in the surgical management of these cases is that of whether *spinal fusion* should be combined with removal of the disk protrusion—the so-called “combined operation.” Opinions vary from the extreme that it should be done in every case of disk protrusion, to the other extreme, that it is seldom if ever necessary. Only time and further observation of the results in large numbers of cases can give the answer. For the present it is my opinion that the combined operation should be considered (1) in cases of multiple or recurrent disk protrusions, (2) where there is roentgenographic, clinical or surgical evidence of inherent instability of the lumbosacral spine, (3) where low back pain is severe and disabling for a long period before the onset of sciatic radiation, and (4) where the patient's occupation is one of heavy labor or demands a great deal of lifting.

Obviously the best interests of the patient are served by the full cooperation of neurologic and orthopedic surgeons, and it is no accident that the most advances and the best results in the management of these cases have come from those clinics and institutions where such cooperation is routine and where both the neurologic and orthopedic surgeons have contributed their share to the problem.

**Postoperative Management**—The length of time that a patient should spend in bed after the operation and the period of convalescence before returning to full activity are in my opinion very important points. Since any operative repair of the rupture of the posterior longitudinal spinal ligament or annulus fibrosus is not technically feasible, we are forced to depend on natural means—the proliferation of fibrous connective (scar) tissue—for the repair of these structures and the cavity in the disk left by the removal of fragmented nucleus pulposus and fibrocartilage. It is our practice to keep the patient in bed for two

weeks after the removal of a disk protrusion and then allow gradual resumption of activity. Light work may be resumed in six weeks, full physical activity especially heavy lifting or strenuous work, should be postponed for three months. Some will object to this claiming that such long periods of inactivity tend to destroy the patient's confidence in the result and to increase the number of patients with poor results. It is true, especially in compensation cases, that every effort should be made to discourage the development of an attitude of chronic invalidism. However if an adequate explanation is given the patient for the prolonged convalescence and if, after the prescribed period has passed firm insistence is made on resumption of activity, no serious difficulty should be encountered. Too often a surgeon fails to exercise adequate observation or control of the patient's activity during convalescence and is then disappointed at the patient's refusal to undertake immediate full activity.

## BIBLIOGRAPHY

- 1 Barr, J. S. Sciatica Caused by Intervertebral Disks. *J. Bone & Joint Surg.*, 19:323-342, 1937
- 2 Bradford, F. K. and Spurling, R. G. *The Intervertebral Disk*. Springfield Ill., Charles C. Thomas, 158 pp., 1941
- 3 Dandy, W. E. Loose Cartilage from Intervertebral Disk Simulating Tumor of Spinal Cord. *Arch. Surg.*, 19:660-672, 1929
- 4 French, S. D. and Payne, J. T.. Cauda Equina Compression Syndrome with Herniated Nucleus Pulposus. *Ann. Surg.*, 120:73-87, 1944
- 5 Ingraham, F. D., Bailey, O. T. and Nulsen, F. E. Studies on Fibrin Foam as a Hemostatic Agent in Neurosurgery with Special Reference to Its Comparison with Muscle. *J. Neurosurg.*, 1:171-182, 1944
- 6 Love, J. G. and Walsh, M. N. Protruded Intervertebral Disks. *Surg., Gynec. & Obst.*, 77:497-509, 1943
- 7 Roope, P. G.. Innervation of Annulus Fibrosus and Posterior Longitudinal Ligament. Fourth and Fifth Lumbar Level. *Arch. Neurol. & Psychiat.*, 44:100-103, 1940
- 8 Semmes, R. E., Diagnosis of Ruptured Intervertebral Disk without Contrast Myelography and Comment upon Recent Experience with Modified Hemilaminectomy for Their Removal. *Yale J. Biol. & Med.*, 11:433-437, 1939
- 9 Semmes, R. E. and Murphy, F.. The Syndrome of Unilateral Rupture of the Sixth Cervical Intervertebral Disk with Compression of the Seventh Cervical Nerve Roots. *J.A.M.A.*, 121:1209-1215, 1943
- 10 Spurling, R. G. and Grantham, E. G. Neurologic Picture of Herniations of the Nucleus Pulposus in the Lower Part of the Lumbar Region. *Arch. Surg.*, 40:375-388, 1940

# MANAGEMENT OF MYASTHENIA GRAVIS

RICHARD RICHTER, M D \*

PERHAPS the most gratifying advance in therapy in the field of medical neurology during the past decade has been in the treatment of myasthenia gravis. It is true that the underlying cause of the disease remains unknown and that no cure is in our hands, but the symptomatic relief which the new drugs afford in most cases is nevertheless remarkable. From an era in which all physicians stood virtually helpless before this truly grave and dread malady we have suddenly entered one in which we can not only prolong life and abolish severe distress for our patients but can even achieve a reasonably active life for many of them with considerable assurance. This progress has not been a matter of chance. While one of the important discoveries in the treatment of the disease, the use of ephedrine, was purely accidental, all the rest have resulted from well planned application of knowledge gained in the basic medical sciences, notably in physiology and pharmacology, to practical clinical problems. The whole story of the development of the modern treatment of myasthenia gravis stands as another shining and hopeful example of what may be expected of the intelligent union of theory and practice in the medicine of the future.

It is not intended to leave the impression that the newer methods insure the control of myasthenia gravis or have robbed the disease of all its terrors. For too many patients are refractory to treatment or become so, and either succumb sooner or later to failure of the respiratory muscles and its consequences or are so enfeebled that they are unable to earn a living or even take care of themselves in spite of all that can be done. But comparatively the progress made in treatment has been enormous.

## DIAGNOSIS

A diagnosis of myasthenia gravis can be made in most cases easily and with a high degree of accuracy. In the average fairly well developed case this can usually be done from the signs and symptoms.

**Signs and Symptoms**—*Muscular weakness* is the presenting symptom of disease and, in its various manifestations, the only one. This in itself serves to differentiate myasthenia gravis from a number of neurological conditions in which motor weakness is accompanied by other

---

\* Associate Professor of Medicine, University of Chicago, Attending Neurologist, Albert Merritt Billings Hospital

signs such as muscular atrophy, sensory disturbances or reflex changes. Characteristic of the weakness itself, and always suggestive of the diagnosis is the feature of *fatigability of the affected muscles* during sustained or repeated effort. A facial movement, such as baring the teeth may be done fairly well a few times in succession and then rapidly becomes more restricted until it is altogether impossible. If the weakness is in the upper extremity the hand-clasp at first may be rather strong only to vanish if it is sustained or repeated often. Asked to read or count aloud, a myasthenic patient may do so clearly at the start but soon the speech becomes slurred to the point that words become unintelligible and the voice loses volume until it is no longer audible. Recovery of the original strength usually occurs after a short rest, so that the patients often carry out their tasks by spurts of activity relieved by periods of rest. While the reflexes when first examined are almost always normal, they too, if the responding muscles are involved, may show this same exhaustion when stimulated repeatedly in rapid succession. Not infrequently it is impossible to demonstrate convincingly such sharp development of fatigue during the course of the examination but even in such cases the tendency is apparent in the history. The patient is stronger in the morning after a night's rest and becomes increasingly weak as the day passes, breakfast is eaten with relative ease but lunch and dinner become increasingly difficult to masticate and swallow, or increasing fatigue is noted during the individual meals. A housewife may be able to sweep one room but must stop to rest lest she drop the broom when halfway through the second.

The weakness not only possesses this characteristic quality but in the usual case betrays a characteristic localization as well which is diagnostic in itself. While the muscles of the extremities and trunk are often affected, it is those innervated by the *motor cranial nerves* which are most regularly involved. Among these in particular are the extrinsic muscles of the eyes, producing ptosis of the lids, strabismus and diplopia, the muscles of the face and the muscles of the pharynx and palate with the consequent slurred, nasal speech and choking and regurgitation on swallowing. In the case of all of these muscles the involvement is usually bilateral and more or less symmetrical, although isolated weakness of a single muscle, one external rectus, for example, is not uncommon. In more advanced cases it may also happen that one muscle or a group of muscles becomes totally and permanently paralyzed. This is especially apt to occur with the ocular muscles. The combination of ocular and facial involvement leads to the development of the "myasthenic facies" which is unmis-

takable a smooth, expressionless countenance, rendered drowsy from drooping of the eyelids and stupid from the fallen jaw and partly open mouth occasioned by weakness of the masseter and temporal groups. The lower facial muscles are often weakened in a peculiarly selective way so that in attempting to smile the upper lip is elevated, baring the teeth without retraction of the angles of the mouth. This results in a snarling expression instead of a natural smile, the so-called "risus sardonicus."

**Special Diagnostic Tests**—Even in typical cases it is desirable, and in some early or atypical examples of the disease it becomes necessary, to employ certain special confirmatory diagnostic tests. Of these by far the most useful and important is the prostigmine test.

**Prostigmine Test**—The basis of this procedure rests on the fact that most of the manifestations of myasthenia gravis are improved definitely and promptly by the action of prostigmine, an analogue of physostigmine. In a sense it is a therapeutic test that may be carried out in a few minutes. It is customary to give the patient 1 mg. of prostigmine methyl sulfate subcutaneously. The drug is readily obtainable in ampules for parenteral administration. This dose is ordinarily adequate to produce satisfactory effects without leading to severe side actions. Within fifteen minutes the drug begins to take effect, it reaches its maximum activity in about half an hour and begins to wane after an hour. The patient first experiences a feeling of well-being and renewed strength and soon is able to carry out movements which a few minutes before were well-nigh impossible. The eyes can be opened and diplopia disappears, the patient is able to smile again, the speech loses its thickness and swallowing improves dramatically. The results are often spectacular and seldom fail to astonish the patient and even the physician. Any such clear-cut effect is pathognomonic of myasthenia gravis since it occurs in no other form of muscular weakness. Whether the failure of a decisive response excludes the diagnosis of myasthenia gravis is not so certain, but if such cases exist they are extremely rare. It occasionally happens, however, that some weakened muscle groups respond in this definite way while others, more completely paralyzed, such as the extrinsic ocular muscles, are little if at all influenced by the test. Since prostigmine, like other drugs of its group, is a powerful stimulator of the parasympathetic nervous system, distressing symptoms due to this side action are sometimes produced, especially bradycardia, abdominal cramps and nausea. These are readily controlled by atropine. Consequently it is well to give  $\frac{1}{400}$  grain (0.006 gm.) of atropine together with the prostigmine. It is of interest that while atropine abolishes the auto-

nonic action of prostigmine, it in no way interferes with its influence on the weakness of voluntary muscles

*Curare Test*—Curare when administered to normal subjects in proper dosage produces muscular weakness which closely simulates myasthenia gravis. Myasthenic patients are more susceptible to curare than non-myasthenic persons and experience an exacerbation of their symptoms when given doses of curare too small to be effective in individuals not suffering from the disease. Bennett has utilized this fact to devise a diagnostic test for myasthenia in which the patient is given intravenously one-tenth the dose of standardized curare principle which produces moderate generalized curare asthenia in normal individuals. A positive test consists in the appearance or aggravation of myasthenic signs. Since the drug is difficult to obtain and the procedure potentially hazardous without adding anything of importance to the diagnosis the test is not recommended.

*Quinine Test*—Quinine, like curare, tends to increase the weakness when given to patients with myasthenia gravis and may be utilized in this way to confirm the diagnosis. This, too, because of the unnecessary danger and discomfort to the patient, is not recommended.

*Electrical Stimulation*—The affected muscles of myasthenic patients become fatigued when subjected to prolonged stimulation with an electric current just as they do from sustained volitional or reflex contraction. Instead of the enduring tetanic contraction seen in normal muscles the tension in the muscles fades to nothing during faradic excitation and the muscle does not again respond until a period of rest has intervened. This is the "myasthenic reaction" of Jolly, quoted widely in the textbooks. It forms an interesting sign of myasthenia and is a useful but not a necessary aid in diagnosis. The physician in general practice without the necessary apparatus or experience in electrodiagnosis to carry out this test is at no real disadvantage in the diagnosis of myasthenia.

*Biopsy of Muscles*—In a considerable number of patients with myasthenia gravis examined postmortem the muscles exhibit rather characteristic infiltrations of round cells, resembling lymphocytes. It is sometimes possible to find these so-called "lymphorrhages" in muscle biopsies. But as a diagnostic measure the procedure is cumbersome and uncertain and is rarely if ever needed.

## TREATMENT

*General Measures*—Long before the current drug treatment existed it was recognized that rest is an important consideration in the care of myasthenic patients. For those who exhibit extreme weakness or

show such threatening symptoms as dysnea, periods of complete bed rest may be necessary. Other patients may be well able to do their ordinary jobs, perhaps with the aid of several rest periods distributed through the day. Under no conditions should the patients undertake strenuous physical activity, and programs of exercise or massage are not only useless but may be harmful. It is impossible to outline a regime to fit all patients, since the management of each case must be adapted to the individual circumstances and symptoms. It is a good general rule that patients should pause to rest whenever they become uncomfortably tired and avoid the type or amount of activity which makes them so. Muscle groups which are especially prone to weakness should be spared action so far as possible.

Certain specific symptoms may require attention. Thus, *intractable ptosis* great enough to obscure the patient's vision may be corrected by a support for the upper lid attached to the patient's glasses, a so-called spectacle crutch. Troublesome *diplopia* is best obviated by covering one eye by an eye patch or by pasting Scotch tape over one lens of the patient's glasses. In the case of patients with any appreciable degree of *bulbar weakness*, special attention must be given to the mode of eating. All food must be soft, vegetables puréed, meat ground, and so on, and the patient instructed always to eat slowly and carefully in order to avoid aspiration. In extreme cases feeding by nasal gavage may become necessary. If so the nasal catheter must be introduced with great caution, since it easily passes into the trachea in these patients.

*Acute infections* of all kinds, including the common cold, have a notoriously unfavorable influence upon the course of myasthenia gravis. Every possible precaution should be taken against contracting any infection. When feasible it is advantageous for patients to winter in warm, mild climates.

Formerly it was thought that *pregnancy* exerted a uniformly disastrous effect upon the disease. It is true that many women with myasthenia suffer severe relapses when pregnant. For this reason and because many of them are ill-suited to withstand the physical demands of parenthood it is in general wise for them to avoid conception. However, a number of instances are on record in which the disease has undergone striking remissions during pregnancy. Furthermore, relapses, which according to Viets are most common and severe in the first trimester of pregnancy, can now usually be controlled satisfactorily by drug therapy and therapeutic abortion avoided. This is desirable since abortion itself often aggravates the symptoms and has been fatal.

**Emergency Measures**—Profound weakness or paralysis of the respiratory muscles and aspiration of solids and liquids as a result of weakness of the muscles of the pharynx, epiglottis and glottis are the complications of myasthenia gravis most to be feared. Often these effects are combined and not infrequently lead to sudden and unexpected death. One of the most useful measures for combating such crises is prostigmine administered subcutaneously in doses of 1.5 or 2 mg., repeated as necessary. Every patient should be provided with ampules of prostigmine and a hypodermic syringe and the members of his family instructed in its use in case of necessity. During severe exacerbations it may be necessary to increase the basic dose of prostigmine and to employ not one but several or all of the accessory drugs used in the treatment of the disease, namely ephedrine, guanidine and potassium.

In cases of respiratory paralysis, nasal oxygen may be helpful. At times a respirator is required to tide a patient over such a period. When marked bulbar palsy is a threatening symptom, continuous suction applied to the nasopharynx via a nasal catheter is efficacious in preventing serious aspiration. Prompt bronchoscopy and clearing of the airways can be a life-saving measure after massive aspiration.

**Drug Therapy—Prostigmine**—It can be said that more or less continuous oral medication with prostigmine is by all odds the most dependable and satisfactory means of controlling the symptoms of myasthenia gravis and that it forms the sheet-anchor of the management of most cases. In order to appreciate the rationale of the treatment it is necessary to understand something of the mechanism of the motor innervation of striated skeletal muscle. It is now thought that the transmission of a nerve impulse to the muscle fiber is accomplished by a chemical reaction set up at the motor end-plate of the nerve fiber. The ester *acetylcholine*, is known to be produced at the muscle by stimulation of its motor nerve and there is reason to believe that it is this substance that activates the muscle to contraction. Almost immediately after its formation, acetylcholine is again destroyed by hydrolysis into acetic acid and choline, through the action of a substance known as choline esterase. This insures that the effect of acetylcholine on the muscle is brief, precise and phasic. It has been demonstrated further that prostigmine affects this system by inactivating or inhibiting choline esterase, thus enhancing and prolonging the action of acetylcholine upon the muscle.

From these facts it may be inferred that myasthenia gravis is a metabolic disorder affecting the chemical transmission of nerve impulses to muscles in such a way that the activating effect of acetylcholine is in some way blocked or lessened, and that prostigmine tends



to correct the balance by inhibiting the physiological antagonist of acetylcholine, choline esterase (Fig 33) It is improbable that the fundamental defect of the disease is an excessive concentration of choline esterase at the myoneural junction, since serum esterase con-

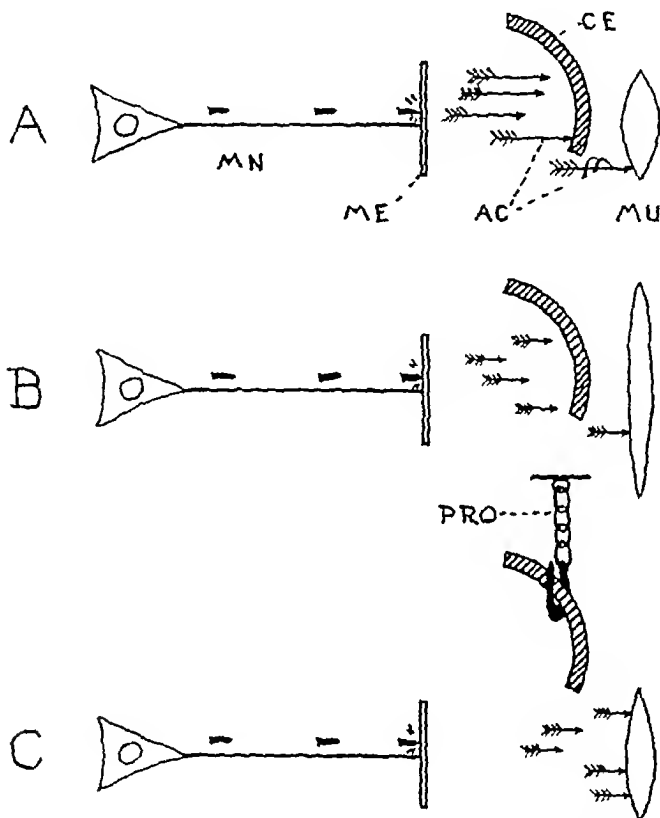


Fig 33—Diagram to illustrate the mechanism of the clinical transmission of nerve impulses to muscle and the mode of action of prostigmine in myasthenia gravis

A represents the normal state where nerve impulses in the motor neuron (MN) impinge upon the motor end plate (ME) releasing acetylcholine (AC), which reaches the muscle (MU) in sufficient amount to produce contraction. The excess acetylcholine is held in check or inhibited by choline esterase (CE).

B represents the situation in myasthenia gravis where the reduced or blocked acetylcholine, indicated by the small arrows, is insufficient to produce muscular contraction.

In C the effect of prostigmine (PRO) is shown. By withdrawing the influence of choline esterase, prostigmine allows enough of the weakened acetylcholine to reach the muscle to give a fairly adequate contractile response.

centrations are no higher in myasthenic patients than in normal controls and show no significant fluctuations with spontaneous changes in the severity of the disease. Choline esterase concentrations in the serum of myasthenic patients do decrease, however, after the admin-

istration of prostigmine and rise again when its symptomatic effects wear off. Whether the primary disturbance of neuromuscular transmission lies in a defective synthesis of acetylcholine or whether the action of acetylcholine on the muscle is blocked by some toxic substance similar to curare is not known.

The effect of parenteral prostigmine on the symptoms of the disease has already been mentioned. *Oral medication*, using the standard tablets containing 15 mg of prostigmine hydrobromide, also alleviates the symptoms, though less promptly and decisively, and is a more satisfactory method of continuous treatment. The effect of an oral dose of the drug begins to be felt within half an hour, reaches its maximum in about an hour and wears off in two or three hours. No

EFFECTIVE DRUGS IN THE TREATMENT OF MYASTHENIA GRAVIS IN ORDER OF THEIR IMPORTANCE AND USEFULNESS

Drug	Dose	Use	Side Actions	Control of Side Action
Prostigmine hydrobromide (Tablets 15 mg.)	60 mg. to 300 mg. a day in 3 to 6 divided doses	Primary control of muscle weakness	Nausea, abdominal distress and cramps, diarrhea	Atropine (1/100 gr 0006 gm.) or 1r belladonna 10 to 15 drops t. i. d.
Ephedrine sulfate (Capsules 3/4 gr)	3/4 gr (0.022 gm.) b.i.d. to t.i.d.	Supplementary to prostigmine	Nervousness, tachycardia and insomnia	Reduce dose or change to another drug
Guanidine hydrochloride (Tablets 125 mg.)	10 mg. to 25 mg. per kilo body weight in 3 or 4 divided doses	Supplementary to prostigmine if not satisfactory	Gastro-intestinal symptoms Nervousness and muscle twitching	Atropine Calcium gluconate
Potassium chloride	10 gm. t.i.d. in evening	Supplementary to prostigmine if not effective	Gastrointestinal symptoms Diuresis	Bismuth subnitrate

fixed rule of dosage can be given. This must be determined individually for each patient. An average dosage for twenty-four hours is 6 or 8 tablets (120 mg.) taken at three-hour intervals. Some patients require much larger doses, up to 20 or 25 tablets (350 mg.). Optimum spacing of dosage is as important as the amount and must also be worked out for each patient. It is usually desirable to give the drug an hour before meals for the advantage it gives in chewing and swallowing. Some patients require a dose on retiring to carry them comfortably through the night. Temporary increase of the basic dosage may be needed to tide the patient over an infection or unavoidable stress and exertion. It is wise to keep the dosage as low as is compatible with reasonably satisfactory results since there is some tendency for patients to experience an increase of symptoms and become re-

fractory to the drug after its effects subside, especially after large doses. Most myasthenics tolerate even large doses of oral prostigmine very well. Those who develop unpleasant symptoms from parasympathetic stimulation should be given tincture of belladonna, 10 to 15 drops with the prostigmine, or, if necessary, atropine,  $\frac{1}{100}$  grain (0.0006 gm). This will control abdominal cramps and other toxic symptoms effectively and rarely needs to be continued more than two or three weeks after medication is begun.

*Ephedrine*—Ephedrine was used for its beneficial effect upon myasthenic symptoms after the accidental discovery of its usefulness by Edgeworth in her own case, several years before the introduction of prostigmine. Fairly satisfactory results were obtained in a number of patients from its use alone. At the present time it is employed chiefly as an adjunct to prostigmine. For most cases it is the most effective supplementary treatment available. It acts to fortify, prolong and smooth out the action of prostigmine. Capsules of ephedrine sulfate,  $\frac{3}{8}$  grain (0.022 gm), given two or three times a day between the doses of prostigmine are usually an effective and satisfactory way to prescribe the drug. Some patients obtain better results by smaller doses given at more frequent intervals. In this case it is convenient to use the prescription recommended by Boothby

Ephedrine sulfate  
Normal saline

gr viii (0.53 gm)  
℥ viii (240 cc)

A teaspoonful of this mixture, which contains a dose of  $\frac{1}{8}$  grain, is given four or five times a day. It is well not to prescribe ephedrine in the evening because of its tendency to produce insomnia, particularly since sedatives should be avoided, if possible, in all myasthenic patients. Amphetamine (Benzedrine), which has other actions similar to ephedrine, gives little or no relief from myasthenic symptoms.

*Guanidine*—Following the experimental demonstration that guanidine increases the sensitivity of muscle to acetylcholine, this drug was used for the treatment of myasthenia gravis. It has a beneficial effect in some, but not all, cases and, like ephedrine, is utilized principally to enhance the action of prostigmine. It is best administered by mouth in tablets containing 0.125 gm of guanidine hydrochloride. As an initial dose, 10 mg per kilo body weight per day divided into three or four doses is recommended. The amount and distribution of dosage must be determined for each patient. Doses of 25 mg per kilo per day can be given safely and doses as high as 45 mg per kilo per day have been employed in severe cases. Myasthenic patients are more tolerant to the drug and less apt to develop toxic symptoms than are

those not having the disease. When such symptoms occur, they either take the form of nausea, abdominal cramps and other gastrointestinal disturbances which are readily controlled by atropine, or appear as nervousness and muscular twitching, which can be counteracted by giving calcium. Guanidine is less reliable and effective, in general, than prostigmine or prostigmine with ephedrine, but may be useful in cases that do not respond well to the latter treatment.

*Potassium*—The use of potassium salts for the treatment of myasthenia gravis was suggested by the fact that potassium increases the effectiveness of acetylcholine on muscle by about 50 per cent and tends to counteract the paralytic action of curare. It is never as effective as prostigmine and cannot be used alone in the treatment of myasthenia with satisfactory results. It may be employed to enhance and prolong the effect of prostigmine and to reduce the prostigmine requirement when ephedrine or guanidine fail to do so. Even for this purpose good results are obtained only with very large doses, that is, 10 to 12 gm of potassium chloride given three times a day. This is one of the principal disadvantages of the treatment since such amounts of potassium lead to very distressing gastrointestinal symptoms and urinary frequency in most patients. The nausea, abdominal distress and diarrhea are best controlled by administering the potassium chloride in some such mixture as the following, suggested by Talbott and Schwab.

1 qt. milk  
1½ cup cream  
1 egg  
2 teaspoonfuls of sugar  
8 teaspoonfuls (30 gm) of potassium chloride

This eggnog is made up daily, kept in the refrigerator and taken in three divided portions. Two teaspoonfuls of bismuth subsalicylate may be added to it. If so, it should be well shaken before taking.

The precise mechanism of the effect of ephedrine, guanidine or potassium upon the weakness of affected muscles is not well understood. It evidently does not depend upon inhibition of choline esterase as is the case with prostigmine.

*Glycine*—Amino-acetic acid (glycine) has been reported to be beneficial and has been used extensively in the treatment of myasthenia gravis, especially before the advent of prostigmine. It is given customarily in doses of 20 to 30 gm a day preferably in milk. In my experience it has never been effective except when ephedrine or prostigmine has been given at the same time and it is my opinion that it is of no benefit whatever.

**Endocrine Therapy**—Inasmuch as myasthenia gravis can now be classed as a metabolic disease, and as it often shows striking fluctuations in relation to menstruation and pregnancy and there are reasons to believe that it may be related to some hypothetical activity of the thymus gland, it is only natural that many attempts have been made to treat the disease with a wide variety of endocrine substances. These include thyroid extract, thymus extract, adrenal cortical substance, antophysin, estradiol dipropionate, testosterone propionate, progesterone and other sex hormones. There is almost general agreement that none of these substances is of value in myasthenia.

**Surgical Treatment**—During the past few years increasing interest has been attracted to the treatment of myasthenia gravis by the removal of a persistent or hyperplastic thymus gland or occasionally a thymic tumor. The lead to this approach in therapy has been taken from the pathological experience that about half the cases of myasthenia gravis that have come to autopsy have shown some abnormality of the thymus, either in the form of hyperplasia, benign thymoma or, rarely, malignant thymic tumor. Thus, of ninety-five instances of lesions of the thymus in myasthenia gravis found at operation or autopsy, forty-two were classified as simple hyperplasia, forty-seven as benign thymoma and six as malignant thymoma. It should be borne in mind, however, that from the pathological standpoint the distinction between hyperplasia and benign thymoma is not a sharp one and that there is no histological uniformity in the type of thymic hyperplasia encountered in myasthenia gravis. In some cases this appears as an increase of epithelial tissue, in others as proliferation of the lymphocytic elements of the thymus.

The early attempts at thymectomy, beginning with that of Sauerbruch in 1912, were disappointing from an operative standpoint. Modern technical developments in thoracic surgery and improved methods of postoperative care have made possible successful thymectomies in a small but notable series of myasthenic patients. In twenty-eight thymectomies reported in the recent American literature there were only five deaths. This is an excellent record if one considers the fact that patients with myasthenia are, in general, poor surgical risks.

Following the operation there appears to have been striking improvement in a number of the patients, amounting virtually to a cure of two to three years' duration in a few. When the case histories of the twenty-three patients who survived the operation are examined critically, and even when the cases recorded as only moderately improved are excluded, there remain seven who are obviously much better and do well on greatly reduced doses of prostigmine and five

who lead normally active lives with little or no medication. Such reports must be judged with great caution and even skepticism in view of the tendency which the disease sometimes shows for long spontaneous remissions. Moreover it would appear most unlikely that abnormality of the thymus is the primary or essential basis for the disease, when only half the cases show any thymic abnormality and some cases are in no way influenced by removal of the thymus. Nevertheless, the prompt and decisive improvement of symptoms almost immediately following operation in so many cases and the completeness and duration of the postoperative remissions in some cannot be disregarded. This form of treatment is still in the stage of trial and many more cases will have to be studied and longer postoperative periods elapse before its true worth can be estimated. It is a treatment, also, which can be undertaken satisfactorily only by experienced thoracic surgeons. It appears that patients with actual tumors of the thymus are more apt to receive marked benefit from the operation than those with simple hyperplasia. If one can speak of indications for the procedure at this stage of its development, it seems that one would choose patients in whom an anterior mediastinal tumor can be diagnosed by x-ray or patients who remain seriously incapacitated by the disease in spite of adequate medical management. Ordinary thymic hyperplasia can rarely, if ever, be diagnosed by x-ray and even thymic tumors may be extremely difficult to demonstrate and require careful fluoroscopic study and lateral chest films in addition to the usual ones.

Roentgen therapy of the thymic region has been carried out in many cases of myasthenia gravis with most conflicting and inconclusive results. There would seem to be no contraindication to trying it.

#### SUMMARY

Myasthenia gravis is to be regarded as a metabolic disease in which the transmission of the motor nerve impulse at the myoneural junction is blocked by interference with the action of the transmitter acetylcholine, upon the muscle fiber. The disease is characterized by rapid, more or less reversible muscular exhaustion and weakness or even by paralysis which selects by preference the bulbar and ocular muscles. Consequently the cardinal signs are those of ptosis, strabismus, diplopia, dysarthria, dysphagia and difficulty in chewing. The diagnosis can be established with a high degree of certainty by the prompt and decisive improvement of symptoms induced by prostigmine. One milligram of prostigmine methyl sulfate is used subcutaneously for this purpose.

The most satisfactory medical management for the average case consists in the oral administration of prostigmine hydrobromide in doses of from 60 to 200 mg a day in divided doses. The optimum dose and its spacing must be determined for each patient. Often the prostigmine can be supplemented to advantage by ephedrine, guanidine or potassium.

General hygienic measures, in particular the avoidance of undue physical exertion and strain, form an important part of the therapeutic regime of every patient.

Roentgen irradiation of the thymus gland is of questionable value but it probably is worth a trial, at least in cases refractory to medical measures. In selected cases surgical removal of the thymus gland may be considered.

## PERIARTERITIS NODOSA

GEORGE W SCUPHAN, M.D.\* AND JANET R KINNEY, M.D.†

### PRESENTATION OF A CASE

This patient was admitted to the hospital complaining of a sprained ankle of three weeks' duration. Additional complaints were fever, weakness and increasing difficulty in breathing for two months. She had had numbness and burning pains in both the right foot and hand. Her family was concerned about the swelling of her face and eyelids which had become quite marked.

The patient had been under observation as an ambulatory patient for a year and a half prior to this admission. When she first consulted us, she said that she had had hypertension for eleven years and the symptoms suggestive of angina of effort for a year. Her main complaint was difficulty in breathing. On frequent observations her blood pressure was slightly elevated and varied from 140 to 164 systolic and 100 to 110 diastolic. There was moderate enlargement of her heart but no other significant findings. Her chest was emphysematous, and the breath sounds were characteristic of a mild asthmatic bronchitis. This became really troublesome only when complicated by acute respiratory infections. The allergic factor was corroborated by an eosinophilia of 8 per cent and the finding of nasal polyposis. Following removal of the polyps, and on other treatment directed at her pulmonary pathologic condition, she improved and was able to carry on normal activity. In February of 1944 she went to the southwest. Her white blood count at this time was 9600 with 8 per cent eosinophils. Six weeks later in New Mexico, because of the appearance of low fever and increasing asthma, her count was rechecked and found to be 19 000 leukocytes with 65 per cent eosinophils. No other abnormal cells were noted. Shortly after this she developed the weakness, numbness and pain in the foot which brought her to the hospital.

On admission to the hospital *physical examination* revealed a moderately ill 55 year old white female. There was periorbital edema of the lids. The eye reflexes and extraocular movements were normal. The eye grounds showed mild hypertensive retinopathy with only minimal nicking of the veins. The nasal mucous membranes were pale and boggy. The throat and pharynx were normal. The thyroid was not enlarged. The chest was emphysematous in contour and expiratory wheezes and loud coarse rales were heard throughout the

---

From the Department of Medicine, St. Luke's Hospital, Chicago.

\* Associate Professor of Medicine, Northwestern University Medical School.

† Clinical Assistant in Medicine, Northwestern University Medical School.



lung fields The heart was slightly enlarged to the left, the rhythm was regular, the rate 90, tones good, and no murmurs were heard The blood pressure was 130/90 The abdominal findings were essentially negative There was a right footdrop, the right ankle jerk could not be elicited and the right knee jerk was diminished There was no sensory impairment, and no muscular tenderness The bones and joints showed no abnormality

The most significant *laboratory finding* was a white count of 38,600 with 61 per cent of eosinophil leukocytes On repeated counts eosinophilia was always over 45 per cent There were no immature or abnormal forms The red count was 4,860,000 and the hemoglobin 14.6 gm, anemia has never been a factor Urinalyses were repeatedly normal There was no nitrogen retention The spinal fluid findings were normal

*X-ray examination* of the chest revealed a heart of approximately normal size The appearance of the lung fields suggested emphysema, with an increase in peribronchial markings with linear striations all the way to the chest wall The diaphragm was low and nodular Gastro-intestinal x-ray examinations were without significance

An *electrocardiogram* revealed no significant deviation from the normal other than left axis deviation with depression of the T waves in the precordial leads only This pattern has been unchanged during the period of observation

*Examinations of the stools* at numerous intervals because of episodes of diarrhea were unrevealing except that on several occasions enteromonas hominis were reported At no time was blood encountered, nor was there other evidence of bleeding *Sputum examinations* showed eosinophil cells, but no constant characteristic organism Clotting activity, bleeding and coagulation times were normal

The *sedimentation rate* of the erythrocytes was 32 mm per hour

Because of the marked eosinophilia, periorbital edema which was striking, and some diarrhea, trichinosis was considered the probable cause of her symptoms An intradermal test with trichinella extract produced an immediate well marked wheal reaction Even though there was no definite muscle tenderness, and in spite of the mild localized peripheral neuritis, the diagnosis of trichinosis seemed to be justified The patient was discharged after a stay of fifteen days in the hospital During this period, her temperature showed a daily average rise to 100° F Her asthma improved under the therapy employed and the patient was told that she would improve spontaneously as patients with trichinosis usually did

However, instead of the improvement expected, the patient became more and more uncomfortable The peripheral neuritis became more annoying Footdrop developed in the other foot, and became complete in the left so that the patient could not walk Numbness and burning pain in the left hand became almost unbearable She became emotion-

ally unstable, and wept because of the progressive increase in her symptoms. The asthma became worse, and after a few days almost intractable. Diarrhea of mild severity again made its appearance.

The patient was readmitted to the hospital after about one month at home during which time she had failed considerably. There was a daily rise in fever to a maximum of  $102^{\circ}$  F which showed a gradual decline with improvement in the asthmatic state. This was best controlled by the intramuscular injection of aminophylline in doses of  $3\frac{3}{4}$  grains (0.23 gm) at four-hour intervals. The amount of sputum was large, and with the increased bronchial drainage, the temperature declined to a level below  $100^{\circ}$  F. One subsequent rise to  $103^{\circ}$  F for a few days seemed to be associated with an episode of respiratory infection and exacerbation of asthma. Other than this, the only symptoms were intermittent diarrhea and those associated with the increasing severity of the peripheral neuritis.

In view of the protracted course, the eosinophilia, the increasing prominence of the neurologic findings in the absence of any marked muscle tenderness, and the evidence of involvement of cardiac, pulmonary and gastro-intestinal symptoms the diagnosis of periarteritis nodosa was considered. The patient submitted to muscle biopsy. At operation there was no evidence of inflammation. The gastrocnemius muscle was purple in color rather than red, and appeared flaccid. A portion of this muscle was removed and an additional portion from the soleus.

The *histology* of these tissues was reported by Dr. Edwin F. Hirsch as follows: "The tissues from the left soleus muscle have the usual skeletal muscle fibers and supporting fibrous stroma with a little fat. There is no acute exudative inflammation of the muscle tissues proper nor are trichina larvae present. The walls of the medium sized arteries have an acute or subacute exudative inflammation, distributed in varying degrees mainly in the outer portions of the wall. This exudative inflammation consists of infiltrations of polymorphonuclear leukocytes, most of them with eosinophil granules, a few lymphocytes and small numbers of fibroplastic cells. These reaction changes are not distributed uniformly. At levels of rather marked changes, the inflammation involves considerable of the perivascular stroma and other adjacent structures. The tissues from the gastrocnemius also have skeletal muscle fibers without trichina larvae. There is an acute or subacute exudative inflammation of varying intensity of the outer portions of the walls of the medium sized arteries."

*Neurologic examination* by Dr. R. P. Mackay was recorded on May 27, 1944. There were no cranial nerve palsies, but poorly sustained nystagmus on lateral gaze right and left. Left wrist drop was present, with good grip. Flexion and extension of the elbows and pronation and supination were normal on both sides except supination on the right. There was right footdrop with marked weakness of ankle ex-

tension on the left All proximal movements in the lower extremities were powerful Reflexes were good in the upper extremities Knee jerks were barely elicitable, and the left ankle jerk was similarly reduced, the right was absent All hamstring reflexes were good No pathologic reflexes were noted, nor was there any sensory impairment There was remarkably little tenderness of the extremities

Dr Mackay's comments were "The significant neurological feature is the discreteness of the peripheral neuritis, that is, the disseminated severe peripheral nerve lesions with other well preserved peripheral nerves"

*Treatment* of this case has been largely symptomatic Asthma was controlled by use of aminophylline parenterally For the diarrhea kaolin, belladonna, paregoric and vioform were used from time to time all with some success Thiamine hydrochloride was given in large amounts

Because of the exudative character of the disease it was decided to use large amounts of sodium salicylate These the patient tolerated well even in amounts up to 10 gm daily

Orthopedic measures for the control of footdrop have been helpful in preventing contractures and in the comfort of the patient Light removable plaster splints, comfortably padded, support both feet

The *subsequent course* has been that of slight improvement The neurologic findings have remained essentially the same, there has been no further loss of function, in fact, some movement of the toes of the right foot, the one first involved, has been noted The subjective symptoms of numbness and paresthesias have not been so conspicuous a part of the daily complaints, and in the hand have largely subsided The asthma is still an occasional problem but is fairly well controlled at present Although we have controlled the infestation with *enteromonas hominis*, there are still occasional episodes of frequent loose stools

In general the patient's condition has improved, at least the disease seems to be no longer progressive although the feature of leukocytosis with marked eosinophilia persists She is at home, able to be up in a wheel chair

#### COMMENT

There are several features of this case which are of particular interest The first is that of marked eosinophilia, which with the periorbital edema originally led to the erroneous diagnosis of trichinosis The positive and quite characteristic skin test with the trichinella antigen was confusing It cannot be readily explained unless the view can be accepted that periarteritis nodosa is a disorder manifested by

extreme sensitization which becomes general because of its intensity.<sup>1</sup> The extreme eosinophilia is evidence of this. Such an experience as this would suggest that muscle biopsy be done in each case in which trichinosis is suspected. It is easily done, and it requires no special technique to demonstrate the organisms. They are to be seen in fresh tissue without staining when the muscle fibers are compressed between two fairly heavy pieces of glass. These are examined under the low power of the microscope.

**Incidence**—Periarteritis nodosa has been considered a rare disease. Until 1935 about 150 cases had been reported, twenty in the American literature.<sup>2</sup> Since then numerous cases have been reported each year so that the total number is many more than twice the figure given. That the disease is much more common than the case reports indicate must be true. Many cases are no doubt unrecognized since the clinical pattern so often is characterized by visceral manifestations of wide variety. Most often when the diagnosis has been made, it has been at autopsy, and in the total deaths in the United States postmortem examination is exceptional. No doubt, since recovery has been reported, many more cases escape recognition.<sup>3</sup>

**Etiology**—The etiology of the disease is obscure, and a wide variety of theories as to its cause have been advanced. Many cases have been associated with infection<sup>4, 5, 6</sup> as well as with rheumatic fever.<sup>7</sup> The clinical association of the disease with bronchial asthma has been most frequently commented on<sup>7, 8</sup> and the frequency with which high eosinophil counts occur also lends support to this view. The work of Rich<sup>1</sup> on hypersensitization adds weight to this theory. Krupp<sup>9</sup> has noted the similarity between this disease and lupus erythematosus, Libman-Sachs disease and rheumatic fever. All seem to present some manifestations of tissue sensitivity, each in a different way. In the present case, allergy has been a constant manifestation, whether a causal or coincidental factor, it is not possible to say. The frequency with which asthma has been reported suggests that it is more than coincidental. It is possible that it may be a visceral manifestation that is, merely a manifestation of a vascular disease affecting the pulmonary structures.

**Pathology**—The pathology is well established. Arkin has described four stages: (1) the alterative degenerative or beginning stage, (2) acute exudative inflammatory stage, (3) the stage of granulation or healing, (4) the stage of fibrotic scar tissue or end stage. Our case would fall into the second stage of Arkin. Karsner<sup>10</sup> found that necrosis and exudation are the most frequent types of pathologic change seen in the vessels. In typical cases the cells of the exudate include

both polymorphonuclear and mononuclear eosinophils. As a result of necrosis in the vessel walls, hemorrhage may occur, and small aneurysms frequently are a characteristic feature. The disease is one of the vascular system, specifically of the arteries. Hence, the same lesions have been noted in every structure of the body, sometimes predominating in one location or organ, sometimes, as in this case, in the peripheral vessels.

This wide dissemination would account for the great variety of clinical manifestations. Most accounts have emphasized involvement of the heart, kidneys, lungs, abdominal viscera, particularly frequent have been the manifestations of renal disease which are absent here. Carr<sup>11</sup> reported a case which was essentially limited to the lower extremities and in which gangrene developed early. This is most unusual. The symptoms in each case are those which occur as a result of disturbance in function of the viscera or structures involved by the pathological process.

That this case presented cardiac involvement is evident. One of the initial complaints was that of mild angina of effort and it was this which led the patient to seek medical aid. Pulmonary disease in the form of asthma has been a prominent symptom. The patient has had diarrhea of undetermined origin. True, there was another explanation for it, but the diarrhea has persisted in spite of the control of this factor. There were no abnormal findings in the colon x-ray, and sigmoidoscopy was not done. Felsen<sup>12</sup> made the diagnosis by sigmoidoscopic examination in one case prior to death. He noted peculiar horizontal linear dark red streaks running in parallel lines in the rectosigmoid area. Careful study with a telescopic device revealed that these lesions were within the vessels. Examination at autopsy confirmed those findings.

Attention has been called to the frequency of pains in the arms and legs, particularly tenderness as an outstanding group of symptoms. These were absent here, but certainly there were equivalent symptoms of nerve involvement in the numbness, tingling and burning sensations of which the patient complained so bitterly. Peripheral neuritis has been described, but not as a frequent feature of the disease.<sup>7</sup> Kernohan and Waltman<sup>13</sup> reported five cases in which the neurologic features of the disease were emphasized. Involvement of the peripheral nerves was quite common in this group. Cranial nerves may also be involved, and therefore, blindness, diplopia, deafness, facial paralysis and dysphagia may be part of the pattern. The central nervous system may also be involved, and this has frequently been re-

ported (cerebral hemorrhage and thrombosis have been particularly common

The anatomical association of the peripheral nerves with the arteries and veins in the same sheath in the extremities explains the occurrence of peripheral neuritis in this case. Obviously, the inflammatory reaction in the walls of the arteries extended to involve the adjacent peripheral nerves wherever the inflammatory reaction was extensive. Dr. Hirsh noted the tendency of the exudate to occur in localized regions along the course of the vessels. This would then also account for the isolated nerves involved, quite in contrast to the general peripheral neuritis of deficiency or toxic disease.

**Diagnosis**—The diagnosis in this case should, and could, have been made much sooner had we not been led astray by the idea that trichinosis offered the best explanation. It was proper to consider it in the diagnosis but this patient presented at the time of her first admission to the hospital all the features characteristic of periarteritis nodosa in that she had the involvement of multiple structures throughout the body so characteristic of disseminated vascular disease. She did not have all of them, but in connection with fever, leukocytosis, eosinophilia and allergy, the clinical pattern was fairly complete.

If we bear this pattern in mind, the clinical diagnosis of this disease can be made more frequently. When skeletal muscle involvement can be demonstrated, the diagnosis can be confirmed by biopsy with relative ease.

**Treatment**—Treatment of this disease must of necessity be symptomatic, first, because its etiology is not known and, second, because of the wide variety of symptoms requiring control for the comfort of the patient. This is well illustrated in the present case by the anginal syndrome, asthma, enteritis and peripheral neuritis. The only therapy which could be considered to have any bearing on the characteristic pathologic findings was the use of sodium salicylate. This drug was given because of the exudative character of the disease, and its similarity in this respect to rheumatic fever.

The results of therapy are difficult to evaluate because of the uncertainty of the clinical course, which often consists of natural remissions and exacerbations, the remissions in particular may continue for months or even years.<sup>4</sup> It is therefore, not reasonable to conclude that the improvement noted thus far in this case is the result of salicylate therapy, but it appears to be rational, and seems to have contributed to the comfort of the patient, at least.

The ultimate outcome of any case of periarteritis nodosa is uncer-

tain, apparently some patients recover, but the vast majority of reported cases have terminated fatally

### CONCLUSION

In conclusion, it can be said that periarteritis nodosa is a disease of the vascular system, particularly the medium sized arteries. The symptomatology is dependent upon the viscera, or structures involved, and these are usually multiple. Asthma is often associated. Eosinophilias of varying degrees are common. Its course is extremely variable, and its prognosis uncertain, most reported cases have terminated fatally. The diagnosis may be made clinically if the essential character of the disease is borne in mind.

### BIBLIOGRAPHY

- 1 Rich, A. R. Additional Evidence of Hypersensitivity in the Etiology of Periarteritis Nodosa. *Bull. Johns Hopkins Hosp.*, 71:375 (Dec.) 1942
- 2 Haining, R. B. and Kimball, T. S. Polyarteritis Nodosa. *Am. J. Path.*, 10:349 (May) 1935
- 3 Mottley, L. Periarteritis Nodosa. *J.A.M.A.*, 106:898 (March 14) 1936
- 4 Arkin, A. Clinical and Pathological Study of Periarteritis Nodosa. Report of Five Cases, One Histologically Healed. *Am. J. Path.*, 6:401, 1930
- 5 Manzer, F. and Joël, W. Periarteritis Nodosa as a Manifestation of Sepsis Lenta Due to *Streptococcus Viridans*. *Acta Med. Scandinav.*, 85:397, 1935
- 6 Friedberg, C. K. and Gross, L. Periarteritis Nodosa (Necrotizing Arteritis) Associated with Rheumatic Heart Disease. *Arch. Int. Med.*, 54:170 (Aug) 1934
- 7 Spiegel, Rose. Clinical Aspects of Periarteritis Nodosa. *Arch. Int. Med.*, 58:993 (Dec.) 1936
- 8 Cohen, M. B., Kline, B. S. and Young, A. M. The Clinical Diagnosis of Periarteritis Nodosa. *J.A.M.A.*, 107:1555 (Nov. 7) 1936
- 9 Krupp, M. A. Urinary Sediment in Visceral Angitis (Periarteritis Nodosa, Lupus Erythematosus, Libman-Sachs Disease). *Arch. Int. Med.*, 71:54 1942
- 10 Karsner, H. T. Primary Inflammation of Arteries. *Ann. Int. Med.*, 11:164, 1937
- 11 Carr, J. G. Periarteritis Nodosa. *M. CLIN. NORTH AMERICA*, 13:1121, 1930
- 12 Felsen, J. The Sigmoidoscopic Diagnosis of Periarteritis Nodosa. *Ann. Int. Med.*, 15:251 (Aug.) 1941
- 13 Kernohan, J. W. and Waltman, H. W. Periarteritis Nodosa. *Proc. Staff Meet., Mayo Clinic*, 12:554, 1937

# THE MODERN CONCEPT OF SCHIZOPHRENIA

L. J. MEDUNA, M.D.,\* AND W. S. McCULLOCH, M.D.†

IN contemporary psychiatry, schizophrenia is the misleading and misused name of most perplexing mental diseases. The difficulty in distinguishing the diseases has led to an ever widening application of the term until it now embraces all but a few mental disorders. Today such symptoms as catatonia or delusions or ideas of reference have become synonymous with schizophrenia. All this has happened since 1910, but to understand the difficulty we must go back into the history of psychiatric ideas.

## VESANIA

Prior to the beginning of our psychiatry, physicians had distinguished four kinds of mental derangements: (1) mental enfeeblement, due to organic diseases, (2) partial madness, including *paranoia vera*, *neuroses* and *hysteria*, (3) *delirium*, or total madness associated with fevers, and finally, (4) the *vesania*, or total madness without *delirium* or fever. Modern psychiatry began with the conception of a psychosis as a disease consisting of a threefold unity—one etiology, one symptomatology, one course. In 1851, Falret<sup>1</sup> described (1) *folie circulaire*, now called the manic-depressive psychosis. In 1868, Sander described (2) *paranoia*. In 1874, Kahlbaum<sup>2</sup> published a description of (3) *catatonia*, and Hecker, who had collaborated with him for eleven years, that of (4) *hebephrenia*. There remained (5) *vesania typica*, characterized by fragmentary and fading delusions and a lack of appropriate feeling or emotion, and (6) *dysthymia*, consisting of *melancholias* and profound psychoneuroses.

To any one familiar with these descriptions of *hebephrenia* and *catatonia*, it is scarcely necessary to say that those diseases bore little resemblance to the cases now diagnosed *catatonic* or *hebephrenic schizophrenia*. *Catatonia* and *hebephrenia* began with a period of depression passing into excitement. Then came the symptoms that gave them their names. Thereafter, the *catatonics* frequently died. If not, they either remained demented or remitted, whereas the *hebephrenics*

---

From the Department of Psychiatry, University of Illinois College of Medicine, and the Illinois Neuropsychiatric Institute, Chicago. This investigation has been aided by a grant from the Josiah Macy Jr. Foundation.

\* Associate Professor of Psychiatry, University of Illinois College of Medicine, and the Illinois Neuropsychiatric Institute.

† Associate Professor of Psychiatry, University of Illinois College of Medicine, and the Illinois Neuropsychiatric Institute.



regularly went into a silly dementia which was usually complete within eighteen months. Both diseases were characterized from the outset by a loss of affectibility—i.e., the patient's feelings and emotions were not determined by what happened to him or to those for whom he had cared.

*Kahlbaum's* greatest contribution was that he separated, out of the *vesania*, the *dementia paralytica*. This makes it permissible to refer to all the derivatives of the *vesania* as functional diseases. Such was the psychiatry which both *Kraepelin*<sup>3</sup> and *Adolph Meyer*<sup>4</sup> inherited. Their reactions to it were opposite. Disgusted by the perplexing mixture of symptoms and their fluctuations, which made diagnosis of psychoses the most difficult and fallible of the arts of medicine, *Adolph Meyer* produced a perfectly consistent and universally applicable system of nomenclature based on the most prominent psychobiological features of his patients' disorders. The holistic implications of this Linnaean classification have bridged the dualistic chasm in psychiatry for many an unsuspecting Cartesian and prepared physicians for psychoanalytic emphasis on interpersonal relations. Unfortunately, the biology was not pushed analytically into pathophysiology to determine the significant physical or chemical changes in any form of *vesania*. Being purely descriptive, it presented no obstacle to the spread in the use of the supposedly interpretive term *schizophrenia* to any and all types of *pathergasias*.

*Adolph Meyer's* antipathy to the *Kraepelinian* approach is probably best put in his own words: "The man who did not know or mind the fact that he diagnosed wrongly two out of every three cases stamped by him as *paresis* undertook to tempt the world into thinking in terms of a diagnostic wish-fulfillment, so as to jump from one type of confusion and complacency into another type of confusion and challenge. Instead of letting medical progress and mastery of facts and destiny lead, *Kraepelin* satisfied himself and large numbers of physicians with the interest in end-results and flattery of the power of fortune-telling, and the challenge of a unitary conception for the problem of deficiency formation, in other words, the problem of bankruptcy of both patient and physician."

#### DEMENTIA PRAECOX

Yet it is to *Kraepelin's* insistence on the "unitary conception of deficiency formation" that we must now look for the description of the fundamental traits from which the conception of *schizophrenia* evolved. It is not to be found in *Kraepelin's* first book, published in 1883, in which the classification lacks unity—etiologic, prognostic or

pathologic. Although it calls attention to heretofore neglected aspects of psychoses, it adds little to the nosology inherited from Kahlbaum. But in the fourth edition, 1893 the triadic unity of a psychosis appears. His description of dementia praecox, a term previously used by Morel for another condition, remains one of the few unmoved foundation stones of psychiatry. Here for the first time are made those distinctions which Bleuler used later in defining schizophrenia. Dementia praecox, in the fourth edition, appeared in place of hebephrenia in the same rank as catatonias. Only later did it include the catatonic, paranoid and simple types with the hebephrenic under a single caption, and then only because Kraepelin was convinced that they had the same etiology, course and defining symptomatology. He originally thought that there must be a degenerative pathology but in 1896, he termed it a metabolic disturbance of as yet unknown nature. Because of the invariable outcome "permanent peculiar enfeeblement," he gave it the name dementia praecox. He says, "We are able now, at the beginning of an illness, to predict its resulting in a characteristic state of feebleness."

To do this required, first, that one distinguish between transitory and fundamental symptoms, for the diagnosis rested on two and only two, fundamental symptoms. In 1893, Kraepelin said "Compared with these, all other disturbances, however prominent they may be in individual cases must be regarded as merely transitory and therefore not absolutely diagnostic features. This holds good, for instance, of delusions and hallucinations, which are frequently present, but may be developed in very different degrees or altogether absent or disappear, without the fundamental features being in any way affected."

The core of the disease is a specific deterioration characterized by these two fundamental symptoms, "the peculiar and fundamental want of any strong feeling of the impressions of life" and "impaired ability to understand and to remember," which amounts to "a weakness of judgment and flightiness although pure memory has suffered little if at all", and again "We have a mental and emotional infirmity to deal with—the infirmity is the incurable outcome of the disease." By "mental infirmity" or "feebleness of judgment," it is clear that he did not imply any deficit of information or comprehension, but rather a disorder of evaluation, and similarly, by "emotional infirmity" that he did not imply a want of feeling and emotion, but rather a lack of interest and affection, for he says, "the faculty of comprehension and the recollection of knowledge previously acquired are much less affected than the judgment and especially than the emotional impulses and the acts of volition which stand in closest relation to those in

pulses The complete loss of mental activity, and of interest in particular, and the failure of every impulse to energy, are such characteristic and fundamental indications that they give a very definite stamp to the condition Together with the weakness of judgment, they are invariable and permanent fundamental features of dementia praecox, accompanying the whole evolution of the disease "

### SCHIZOPHRENIA

From external and internal evidence, it is clear that this description of dementia praecox by Kraepelin was the foundation stone of *Bleuler's* definition of schizophrenia on the tenth page of his first book published in 1911 <sup>5</sup> He says nothing of the etiology in that definition, but specifies the malignant course which never permits "*restitutio ad integrum*" Regarding all other symptoms as accidental, he rests his diagnosis of schizophrenia on what he calls three basic criteria (1) a characteristic disturbance of associations, which is equivalent to the aforementioned weakness of judgment, (2) a disturbance of "*Affektivitat*," comparable to the loss of interest and affection So far the term is almost synonymous with dementia praecox, but to this there is added a third criterion, (3) the lack of primary disturbance of perception, orientation, memory, or, broadly, the lack of any disturbance of the sensorium This third diagnostic criterion, had it been rigorously applied, would have divided the pictures called dementia praecox into two groups, which would, we believe, have been very helpful, but it happened otherwise

The characteristic defect in the association of ideas, according to Bleuler, is their looseness which makes thinking incoherent, incorrect and bizarre or obstructs it altogether If the sensorium be clear, it is difficult to attribute this so-called looseness of associations to anything except disordered valuation, which may ultimately depend upon defective interest and affection This would seem to be indicated by the most careful work done by psychologists and psychiatrists, for it has failed to indicate any formal defect not so explainable

The disturbance of "*Affektivitat*" has been translated by many as disturbance of "affectivity," although no such word is to be found in the Century or the Oxford English Dictionary It is certainly more inclusive than "affectibility," which implies that something matters to the patient From Bleuler's use of the word, it appears to be synonymous at times with emotion, at times with feeling as opposed to reason, and at times with mood, humor or disposition The pathological changes include at least (1) a raised threshold (decreased affectibility or indifference to externals), (2) prolonged latency, (3) abnormal

persistence, (4) lability, (5) incompatibility with concurrent events, (6) incongruities among themselves. Thus, Bleuler's second criterion is less specific than Kraepelin's, which can be translated as loss of "affect," an English word that has been defined as that feeling, emotion or passion which is brought about in us by an (external) influence. From the lack of specificity of Bleuler's second basic criterion springs a part of the difficulty in keeping the term schizophrenia within bounds, for it is difficult to imagine any form of behavior under any circumstances which could not be considered to exhibit a disorder of "Affektivität" to a sufficiently unsympathetic observer. The third criterion, which in itself is excellent, contradicts the assumption that any and all accidental symptoms are irrelevant, for among them Bleuler numbers "hallucinations," "illusions," and "disturbances of perception," each of which, if it be real, implies some disorder of the sensorium. It is therefore not surprising that in the very book which begins with the diagnostic principles, Bleuler, a few pages thereafter, mentions twilight states and dazed conditions and the lack of "Besonnenheit," although "Besonnenheit" in German medicine means exactly the absence of clouding of the sensorium (cf. Lang's German-English Medical Dictionary). Its lack implies a clouded sensorium. Thence the confusion grew so rapidly that the original conception of schizophrenia of 1911 was lost by 1916 when Bleuler's second book appeared. We quote Brill's translation of the fourth edition: "Under schizophrenia are included many atypical melancholias and manias of other schools (especially nearly all 'hysterical' melancholias and manias), most hallucinatory confusions, much that is elsewhere called amentia, a part of the forms consigned to delirium acutum, motility psychoses of Wernicke, primary and secondary dementias without special names, most of the paranoid of other schools, especially all hysterically crazy, nearly all incurable 'hypochondriacs,' some 'nervous people' and compulsive and impulsive patients. The diseases especially distinguished as juvenile and masturbatory all belong here, also a large part of the puberty psychoses and the degeneration psychoses of Magnan. Many prison psychoses and the Ganser twilight states are acute syndromes based on chronic schizophrenia." As if that were not enough, Bleuler specifically includes the paraphrenias of Kraepelin and develops a concept of "latent schizophrenia" which can be brought to light by almost any deleterious external or internal condition. In his own words, "one may never directly exclude schizophrenia." So the term schizophrenia, originally less inclusive than dementia praecox which was but a part of vesania, came to be more inclusive than vesania, perhaps a synonym for crazy.

The confusion is not purely linguistic. Kraepelin and Bleuler and their successors saw cases, now catatonic, now paranoid or hebephrenic. They saw patients who clearly had the defect of judgment and loss of affect become delirious, and delirious patients lose judgment and affect as the sensorium cleared, and others who recovered or even improved upon their premorbid personalities. Any diagnosis implying prognosis was difficult and hazardous. On the other hand, the adjectives catatonic, paranoid or hebephrenic were easy to substantiate and these could all be applied to schizophrenia. So these accidental symptoms usurped the function of the criteria until, today, they are supposed to imply them, and the adjectives imply the noun, schizophrenia. The confusion is now so general that one student of psychiatrists noted "every patient should receive two diagnoses—first schizophrenia, and second, what is wrong with him." One need scarcely add that by the second he did not mean the psychobiological descriptive epithet, but the disease.

It would be difficult, therefore, for this institute to avoid the problem of schizophrenia. It has, in fact, been engaged for nearly a year in the attempt to evaluate Bleuler's original conception of schizophrenia, to sharpen its definition and to distinguish between cases fulfilling that definition and all other so-called schizophrenics, not by artificial classifications, but by conjoined clinical and laboratory observation of recognizable differences.

#### MODERN DISTINCTIONS

The suspicion that these patients suffer from distinguishable diseases began with Kraepelin. In the early twenties, Klags<sup>6</sup> had segregated a group suffering from what he called acute paranoid hallucinosis. They frequently recovered or totally remitted and had an acute onset and a true hallucinosis. These were the cases most frequently cured by "Dauerschlaf." In 1937, Meduna<sup>7</sup> concluded that the cases which benefited from metrazol convulsions had "pseudo" schizophrenia, and suggested that the procedure might separate the "symptomatic" from the "true" or "endogenous" schizophrenias. He had then had three years experience with convulsive therapy and had begun to note clinical differences between the groups, most characteristic whereof was that "symptomatic" cases frequently experienced the disease as a dreadful change which filled them with a fear-like apprehension. This is the "process symptom" of Mauz. They tended to have spontaneous remissions and their good reactions to convulsions were accompanied by an exaggerated shift to the left in the white cell count—i.e., increase of neutrophils and basophils with decrease of eosinophils and

lymphocytes. The "transitory or secondary" symptoms were of no diagnostic value. Meduna, in Amsterdam, christened the recoverable group 'schizophreniform' and Langfeld<sup>8</sup> used this name for them in his monograph where he refers to them as reactive as opposed to genuine, true or endogenous schizophrenia. His diagnostic symptoms are acute onset, a period of cloudiness and evidence of exogenous factors. In 1939, Meduna and Friedman<sup>9</sup> noted that remitting patients frequently described their psychoses as 'like a dream'. The lack of reality of their experiences they compared with that of the theater and spoke of 'feeling as though everyone were playing a part—just acting'. The acute paranoid hallucinosis of Klaesi, the dreadful feeling or process symptom of Mauz, the 'period of cloudiness' of Langfeld and the 'dreamlike' quality of the pathologic experiences of Meduna and Friedman can all be understood if, and only if, there is a disorder of the sensorium. This is exactly what is excluded by Bleuler's third criterion. It separates schizophrenics from these, the remitting, the curable, cases. They are, by Bleuler's definition, not schizophrenics no matter how much they may in other ways resemble them.

To keep the distinction clear in the following instances, we state briefly three postulates:

- 1 Distinguishable diseases may produce indistinguishable pathologies. For diagnosis, one must look to the basic symptoms, not of the ultimate deterioration but of the onset of the psychoses.

- 2 Almost all specific nervous and mental symptoms indicate the location, not the pathological process. Thus, pupillary irregularities, reflex changes, furors, immobility, flexor spasms, echolalia, echopraxia, waxy flexibility and akinetic mutism may appear as a consequence of functional or structural failure of given parts of the brain in any injury or disease of those parts. Any diagnosis based on such symptoms only, is merely anatomic.

- 3 Projection—the attribution of the unwanted to parts of the world other than ourselves—is an essentially healthy reaction. We are all at times guilty of ideas of reference or persecution. The hammer gets blamed for hitting the thumb. The world is suspect to the insecure and the wound that will not heal is damned by the physician. Only depressions show the converse, and the failure to project frequently portends suicide. Regardless of its cause, a projected mental or emotional ineptitude becomes a paranoid trend. This substantiates the defect but does not give any clue to the diagnosis.

Thus, ultimate deterioration, localizing symptoms and paranoid reactions are useless when we wish to know the nature of a disease.

## Case I "Schizophrenia" by Bleuler's Three Criteria

The "true" or "endogenous" schizophrenia as defined by Bleuler is exemplified in the history of Walter, who walked at eleven months, cut his first tooth at one year, was breast fed a little longer and talked at eighteen months. His family attributed his troubles to an automobile accident at three years of age in which he was 'frightened but not injured. His "nonsense talk" began some months later. It made conversation impossible and he was withdrawn from school. He interrupted anyone, screamed, attacked his parents and danced in excitement, but his memory was accurate and extensive. This picture had lasted three years before it brought him, in 1936, to Dr Hamill, to whom we are indebted for permission to publish this abstract from his exhaustive study covering four years.

When first seen, Walter was six years old. His mental age (Binet-Simon) was at least six years, four months and his electroencephalogram was practically normal. His mental content was limited, speech fragmentary, response sometimes incoherent, more often irrelevant, and he repeated instructions before acting on them. Late in November, 1936, presumably because he had heard a rumor about a child killed in an accident in an elevator there, he became terrified when taken to a department store. He trembled, cried, vomited and remained "hysterical" for two days during which time he made little jerking movements of his body and shoulders and said scarcely a word. The following day, Dr Hamill was for the first time able to make out that he failed to distinguish between himself (Walter) and water. Walter shifted to water, thence to Deanna Durbin who played in "Rainbow on the River" and so to water again. Being water, he felt he could not be drowned, but might be imprisoned in the radiator. On hearing the knocking of water in the radiator, he said, "elevator just came up and gave the kid a knock" and again, "they are killing the kid," which terrified him because he was the kid. Then followed, "the telephone burnt and got water after Suzy burnt." (Dr "Where does water come from?") "I come from the show" (Dr "You thought water and Walter were the same thing") "My father used to take me across the river" (Dr "And he called you Walter?") "And got drowned. I do not live on Springfield. Bad boys drink water. They do not drink milk. Good boys live on Springfield. I used to live on Springfield—Mississippi River."

A little later, Walter became much agitated over the telephone which had been "broken off" by the janitor—a confusion of the conversation and the instrument. He had always been afraid of one aunt, and now became irritated with his mother and began biting her. Then followed weeks of incessant questioning. Early in 1937, he had become frightened of movies and began to project his fears on his

brother, Sammy. He produced in drawing and speech, symbols which the doctor had difficulty in understanding. For example, he frequently drew things he called "rabbi" and a series of fifty such were interpreted by him "rabbi eating cock," in which "rabbi" meant "father" and "cock" was "kaka"—for feces. About this time, he began profuse spitting and confused "wash it up" and "wa shit up." His play with water now took the form of drowning anything in reach in the bathtub and pouring water into the family's beds.

During the succeeding year, Walter's behavior improved sufficiently for him to return to school and start to learn spelling. Although he frequently surprised his teacher by his intelligence, he more frequently failed to follow even her leading questions and seemed unable to master thoughts involving more than one sentence. He stood to attention, but always started late and would often smile and laugh to himself. Masturbation began secretly and then publicly. In April, 1940, he was excluded from school. His mental age, which had been above par when he was six, was now at seven, reported as four years, nine months. He failed in practically all tests involving numbers, reasoning, and so forth, and although he could draw a diamond to command, he could not complete the figure of a man lacking head, arms and one leg. On prompting, he drew legs all around it, even protruding from the head. What he learned was by rote and his writing had deteriorated.

We have in this patient gross defects in judgment and a lack of appropriate emotional response without any disorder of the sensorium at any time on record. These are Bleuler's three criteria. It is well to emphasize that it was the distortions in the realm of affection and consideration of others that his parents noted at the beginning of his 'nonsense talk.' This had paralogical traits, namely, the confusion of particulars with generals, of parts with wholes and of symbols with things symbolized, all escaping control by the real world about him. His thinking can scarcely be called more egocentric than belongs to his age, but it is autistic (cf Bychowsky<sup>10</sup>). His initial generalization of a child having been killed in an elevator in a store to all children and all elevators, and so his fear for himself in the store and the subsequent statements about the elevator and the kid, like his confusion of Walter and water in a child who could not spell, seem at first to belong to his age, but to think "I am water so I cannot be drowned," "I am water, water is being pounded in the radiator so I, the kid, and hence some other kid is being pounded in the radiator" is clearly paralogical (cf Domarus<sup>11</sup>). We may put it thus: (1) I am water, (2) water is in the radiator, (3) I am in the radiator, whereas water is only his name, not himself. The obviously false conclusion, for he himself is not in the radiator, is escaped by (1) the "kid" is water



(2) water is in the radiator, (3) the "kid" is in the radiator and by not insisting that it be the same kid. In each case, the error really depends upon a failure to preserve the direction of symbolic reference—from the symbol to the thing symbolized. Water, the name, is not, but only denotes, water, the thing, and he himself, not water, is called "the kid." The extension of water to excretions and the puns thereon only extend the original confusion. The same holds for the rabbit and the cock.

Thus, throughout, there is a primary failure to distinguish between symbols which we can juggle at will in thought and the things meant by those symbols which are what they are and where they are regardless of our thoughts. This is the formal aspect of the defect of judgment and it clearly implies a lack of proper affect. No one to whom the world really matters normally, could make this type of mistake and, conversely, anyone who loses the direction of symbolic reference cannot be normally affected by the world. To account for the coherence observed in trains of thought, associationalistic psychology was forced to introduce the hypothesis of "task" or "Aufgabe," which is but a specification of interest or affection. Its loss may account for the so-called looseness of associations of ideas. For this reason, the resulting intrapsychic ataxia (cf. Stransky<sup>12</sup>) may depend upon some relatively localizable block in the pathways to the region determining that "set" (interest or task), instead of upon a diffuse alteration in the corticothalamic paths subserving the differentiation of our initially general abstractions. Thus, although the defect has a definable form, it does not point unambiguously to any one structure within the central nervous system.

In summary, in this paradigm of Bleuler's schizophrenia, we are confronted with a deterioration of judgment, paralogical in form, and characterized by that type of looseness of association of ideas that always accompanies aimlessness, which, itself, may be but a manifestation of the accompanying deterioration of affection and interest, all of which has occurred without any dreamlike or theater-like or fear-some or clouded state—i.e., with a clear sensorium.

#### Case II Not "Schizophrenia" by Bleuler's Third Criterion

Contrast this case with that of Melvin, eighteen, white, male, one of several healthy children of an outgoing household, an honor student and athlete just graduated from high school. On January 30, 1944, he failed to understand his family's instructions about the car, left it somewhere and could not remember whether he put it into the garage or left it on the street. The next day he was definitely dazed, hesitant in action, then undecided and irritable. That evening, when dressing

to go to a dance, he was confused, nervous and his face was pale and greasy. He returned at 4 A.M. with only a hazy memory of the night. His partner reported that, although he had had nothing to drink, he had seemed drunk and acted so strangely that she had not dared to leave him for a moment. From then, for a day and a night, he talked continuously and so confusedly that his family could not understand him. He grew fearful and hid when people came to the house lest they kill him or he, them. On the fourth day of his psychosis, he was seen by Dr. Rotman from whose pitchy and detailed observations it is evident that Melvin had already become withdrawn and had begun to develop catatonic symptoms rapidly. On the fifth day he appeared so much engrossed in his own thoughts that a logical conversation could not be carried on and he already showed a tendency to refuse food. At this stage he thought that his father had lost his legs that he himself had land-mines in his trousers and he would unbutton them to make sure he had not lost his genitalia. On the sixth day he was admitted to Meyer House where he soon was mute, negativistic, grimacing, sweating profusely and exhibited wax flexibility, echopraxia, dilated pupils with poor reaction to light and, at times, sub-normal temperature. Lumbar puncture, blood sugar level and nonprotein nitrogen were negative. For five weeks he failed to recognize his parents. He carried his hand fearfully thinking it held a grenade. Twenty electric-shock treatments removed his catatonic symptoms and on March 22, 1944 he was discharged symptomatically recovered and with some insight.

Two days later his family called his condition to our attention. There were no delusions, hallucinations, or signs of catatonia, but the formerly warm hearted and loving boy was cool, unmannerly, estranged and selfish. There was no complete blocking but sentences were suddenly interrupted and then completed in a manner at variance with their beginnings. He was not aware that he was ill or that his character had altered. While in this condition of diminished affection and sympathy, or affectability, but without clouding of consciousness, a series of laboratory tests at this institute was essentially normal. The white cell count was then 5000. On April 10, 1944, he became confused, clouded, puzzled and was admitted to the institute where he rapidly became disoriented, apprehensive and, then, thoroughly catatonic. The laboratory tests were repeated and were highly abnormal. The white blood count rose to 11,000, with a shift to the left, reaching 71 per cent polymorphonuclear leukocytes (Bruce<sup>18</sup>). During this phase his mutism and negativism made his ideas unavailable, but on recovery he explained that he had thought himself in London and the street noises were sounds of battle, at another time, that he was in a prison camp that kept changing into a German submarine—and we, his doctors, were its officers.

On April 27 he began to recover and by the first of May he was in

excellent condition Carbohydrate studies were again normal and the white cell count was 5000, with 60 per cent polymorphonuclear leukocytes On May 10 he was discharged with normal ideation, his old affectionate self and with full realization that he had been mentally ill. He has remained well to date

In summary, this paradigm of recoverable cases, resembling schizophrenia in two basic symptoms but not by the third criterion, exhibited five phases First, a sudden onset of clouding of the sensorium with fear-like apprehension and the flavor of a bad dream Second, catatonia, partially concealing hallucinations of being castrated and of holding a grenade in his hand and failure to recognize his family Third, a lucid period during which, despite clear sensorium and very slight ideational difficulty, there was loss of affectibility, and this phase showed normal carbohydrate regulation and blood count (Fig 34) Fourth, again a period of sudden clouding, apprehension and catatonia temporarily concealing disorientation for time, place and person—and this phase showed (a) positive Exton-Rose glucose reaction (i.e. up and again up as in diabetes),<sup>14</sup> (b) a slow blood sugar curve, (c) resistance to insulin (i.e., delayed and diminished), and (d) abnormally large output of anti-insulinic factor in urine, as well as the leukocytosis described by Bruce (Fig 35) Fifth, recovery, a return to the premorbid state—"restitutio ad integrum"—with normal carbohydrate regulation and normal white cell count (Fig 36)

The complete recovery would have excluded the diagnosis of dementia praecox for Kraepelin and, by Bleuler's definition, should exclude schizophrenia

At this time, we do not wish to discuss other tests which were made and may be of localizing and qualifying value or to go into the treatment that may have initiated the final recovery, but it is necessary to point out that this disorder of carbohydrate regulation is not confined to this type of case In fact, a positive Exton-Rose reaction occurs in diabetes, pancreatic or pituitary, and in many so-called affective psychoses Infections produce insulin resistance and leukocytosis What is important is that the clouding of the sensorium was in this as in many another case, covariant with the alteration in carbohydrate metabolism

It is impossible to say whether this case, if untreated, would have remitted spontaneously or would have deteriorated, becoming "dementia praecox" But that even this curable or recoverable case went through the phase of clear sensorium with loss of affection, and some trouble in ideation engenders caution Nothing we have said should be taken to mean that the majority of the old cases of so-called schizo-

phrenia or dementia praecox may not have at one time exhibited a clouded sensorium. The convergence of pathologic processes renders

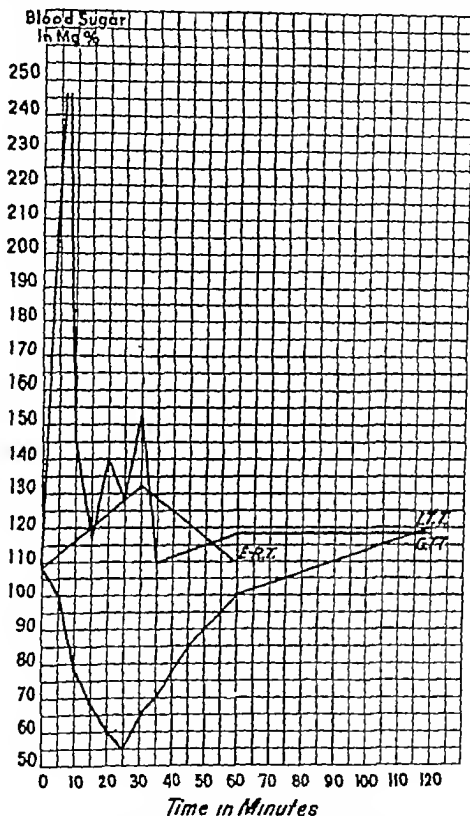


Fig 34.—Phase 3 with unclouded sensorium, all tests normal E.R.T., Exton Rose, 2 dose per os 1 hour glucose tolerance test G.T.T., 0.15 gr per kilogram intravenous glucose tolerance test I.T.T., 0.1 units per kilogram intravenous insulin tolerance test A.I.F., average blood sugar of seven rats (circa 200 gm.) each injected intraperitoneally with one seventh of the total anti-insulinic factor obtainable from a specimen of 24 hour urine.

it likely that many, perhaps most, have done just that. Moreover there is no apparent reason why any case of true schizophrenia may not

subsequently show this clouding—certainly some old cases do. In fact, in 1938, Rumke<sup>15</sup> of Amsterdam reported that a group of such cases treated with insulin or metrazol lost certain symptoms—"transitory" or "accidental" symptoms which frequently imply the clouding of the sensorium—but manifested a progressive shallowing or flattening and

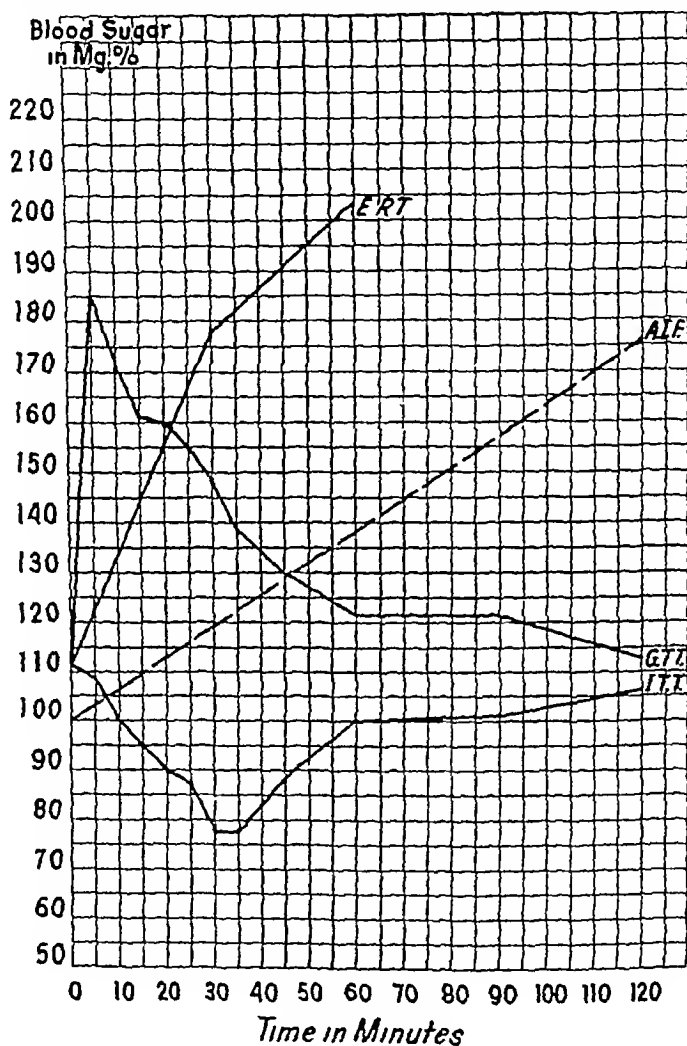


Fig 35—Phase 4, oneiroid process, clouded sensorium, all tests pathological  
Symbols as in Fig 34

a monotony of thought process, briefly, the old schizophrenia remained. One other point must be added to avoid possible misunderstanding. In our limited experience, the changes in carbohydrate metabolism indicated here occur in hebephrenic and paranoid pictures, when, and only when, there is a clouding of the sensorium.

The word sensorium is abbreviated from the Aristotelian term "sen-

sorium commune'—i.e., that place in which from diverse sensations of sight sound and touch, we form our ideas of position and motion and all other 'common sensibles'. That place must obviously be sought among the structures of the central nervous system. The structure is

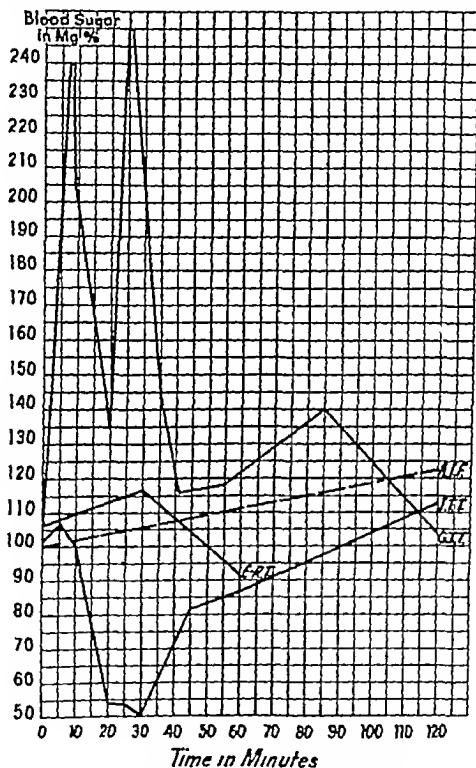


Fig. 36.—Phase 5 restitutio ad integrum, all tests normal. Symbols as in Fig. 34.

only defined for us by its function and it is alteration of that function which is the clouding of the sensorium. But all portions of the central nervous system are alike dependent upon the metabolism of glucose and oxygen. Deficit of either or undue acceleration or retardation of that metabolism must result in alterations of thresholds of

cells and consequently in the relation of their activity to external stimulation. Under given conditions, activity of particular cells implies a specific pattern of activity in cells afferent to them, and so ultimately in the receptors, and therefore a particular pattern in the world impinging upon us. Alteration of thresholds alters these implications so that the same pattern of activity in the cells of the more central structures may correspond to some other configuration of stimulation, and so yield a false inference as to the world. Clouding of the sensorium, disorientations, hallucinations, delusions, failures of perceptions, and a condition resembling dreams, shade into delirium as thresholds shift. If then, as in these cases, there is a gross disorder of carbohydrate regulation, including the presence of an excessive "anti-insulinic factor," it is not surprising to find that life assumes a dream-like quality as the sensorium becomes clouded. Thus, although we would not hazard a guess as to the cause of the metabolic disorder, we do regard the metabolic disorder as a factor in the clouding of the sensorium commune.

#### "ONEIROPHRENIA"

During the writing of this paper, it has become apparent to the authors that to dodge the circumlocution "a - disease - which - has - the - first - two - of - Bleuler's - criteria - but - has - a - clouding - of - the - sensorium - and - therefore - by - his - criterion - is - not - schizophrenia," a name for the disorder is wanted. Certainly "pseudo," "exogenous," "symptomatic," "-oform" and other negations of "true" schizophrenia are cumbersome and senseless or wrong. Moreover, there is current in psychiatric terminology an adjective introduced by Mayer-Gross<sup>10</sup> to describe just such states in which dream and reality mingle. The word is oneiroid—made from the Greek *oneiros*, meaning dream. Beginning in 1588, it has made many compounds to be found in the Oxford English Dictionary. To give the picture its needed name having the right meaning with a minimum of innovation, we shall hereafter refer to it as *oneirophrenia*.

The diagnosis is to be made at the onset of the psychosis, not from the end product. Typically, that onset is acute, sometimes accompanied by alteration of body temperature and leukocytosis, generally manifesting defective judgment and distorted or diminished affect and invariably exhibiting some clouding of the sensorium ranging from mild disorders of perception, defective recollection or recognition, and confusion, to clear hallucinosis, disorientation and a condition verging on delirium. The prognosis is generally good for spontaneous remissions and for those induced by "Dauerschlaf," electroshock or metrazol. The pathophysiology includes at least a disorder of carbo-

hydrate regulation indicated by the pseudodiabetic reaction to the Exton-Rose test, and by the protracted sugar tolerance curves, the resistance to insulin and the presence of an excess of anti-insulinic factor in the urine.

## SUMMARY

Aside from evidence of an increase in anti-insulinic factor in the urine of these patients, there is nothing essentially new in this paper,

## SYNOPSIS

	<i>Schizophrenia</i>	<i>Oniroprenia</i>
	(Def Bleuler Dementia Praecox oder Gruppe der Schizophrenien, in Handbuch der Psychiatrie, edited by G Aschaffenburg 1911, Franz Deuticke, cf pages 10-77)	(Cf W Meyer Gross Selbstschulderungen der Verwirrtheit, Berlin, 1924, pp 101 ff)
Diagnostic Features	<ol style="list-style-type: none"> <li>1 Specific disturbance of associations of Ideas (cf v Domarus Prälogisches Denken in der Schizophrenie, in Zeitschrift für die Gesamte Neurologie und Psychiatrie, Vol. 87, 1923 p 89)</li> <li>2 Specific disturbance of "Affectivity" (cf Kraepelin Lectures on Clinical Psychiatry W Wood &amp; Co 1913 translated from the 3rd German ed., 1904)</li> <li>3 Absence of primary disturbance of sensorium (cf Bleuler, loc. cit., p 10)</li> </ol>	Disturbances of sensorium, evidenced by illusions, confusions, disorientation, loss of contact, true amnesia, benign stupor, true hallucinosis in explicable and involuntary thoughts and feelings inducing dread, weird and frenzied delusions.
Consequent Symptoms	Preposterous, incoherent delusions including pseudohallucinoses predicated upon paralogical thought processes	<ol style="list-style-type: none"> <li>1 Alienation, preoccupation, indifference</li> <li>2 Disrupted, difficult, ineluctable and monotonous thought process.</li> </ol>
Onset	Mostly insidious	Acute or subacute.
Pathophysiology		Disordered carbohydrate metabolism, frequently Bruce's, leukocytosis.
Prognosis	Certain impairment of mental and emotional life with no 'restitutio ad integrum'	All symptoms reversible early, may recover spontaneously or terminate as dementia praecox
Treatment		Interruption of the pathophysiological process by (1) anoxia, (2) Dauerschlaf, (3) insulin (4) metrazol, (5) electrical or any other form of shock.



which was merely intended to sharpen that distinction between two groups of patients which most practical psychiatrists have already separated for themselves. For the convenience of the reader, the diagnostic features, therapeutic indications and prognostic implications are recapitulated in the accompanying table.

In conformity with Kraepelin's and Bleuler's pronouncements, all "transitory" or "accidental" symptoms upon which are predicated distinctions of a type—catatonic, hebephrenic or paranoid—are omitted as useless for the required distinction.

### BIBLIOGRAPHY

- 1 Falret *Responsabilite leg des alienes Extra du dict encyclopaed de Dechambre*, 1876
- 2 Kahlbaum K (a) *Die Gruppierung der Psychischen Krankheiten und die Einteilung der Seelenstörungen*, Danzig, 1863 (b) *Die Katatonie oder das Spannungsirresein*, Berlin, A Hirschwald, 1874
- 3 Kraepelin, E (a) *Psychiatrie*, 2nd ed Leipzig, Abel, 1887 (b) *Lectures in Clinical Psychiatry*, 3rd English ed New York, W Wood & Co, 1913
- 4 Terry, G C and Rennie, Th A C *Analysis of Parergasia*, with an Introduction by Adolph Meyer *Nervous and Mental Disease Monograph Series*, No 69, New York, 1938
- 5 Bleuler, E (a) *Dementia Praecox oder Gruppe der Schizophrenien* In *Handbuch der Psychiatrie*, Leipzig und Wien, Franz Deuticke, 1911 (b) *Textbook of Psychiatry*, English Edition by A A Brill, New York, The Macmillan Co, 1924
- 6 Klati, (a) *Über Somnifern, eine medicamentöse Therapie Schizophrener Aufregungszustände* *Schweiz Arch f Neurol u Psychiat*, Vol 8, 1921
- 7 Meduna, L J (a) *Die Konvulsionstherapie der Schizophrenia* Halle, C. Marhold, 1937 (b) *Vierjährige Erfahrungen mit der Cardiazol-Konvulsionstherapie*, *Psych en Neurol Bladen*, Amsterdam, 1938
- 8 Langfeld, G *The Schizophreniform States* *Monograph*, Kopenhagen, 1938
- 9 Meduna, L J and Friedman, E *The Convulsive-Irritative Therapy of the Psychoses* J.A.M.A., 1939
- 10 Bychowski, G *Physiology of Schizophrenic Thinking* *J Nerv & Ment Dis*, Vol 98, 1943
- 11 V Domarus, E *Pragmatisches Denken in der Schizophrenie* *Ztschr f d ges. Neurol u Psychiat.*, Vol 180, 1923
- 12 Stransky, E *Schizophrenie und intrapsychische Ataxie* *Jahrb f Psychiat u Neurol*, Vol 36, 1919
- 13 Bruce *Quantitative and Qualitative Leucocyte Counts in Various Forms of Mental Disease* *J Ment Sc*, 1904, p 409
- 14 Brace land, Meduna, and Vaichulis To be published
- 15 Rumke *Discussion of paper 7 (b) in Psych en Neurol Bladen*, Amsterdam, 1938
- 16 Mäyer-Gross *Über das Oneiroide Zustandbild, Verslung* *Südwest Dtsch Neurol u Irrenärzte*, Baden-Baden, 1922

## THE FEASIBILITY AND ADVANTAGES OF OUTPATIENT ELECTROSHOCK THERAPY FOR THE MENTALLY ILL

JOHN J. MAODEN, M.D.\* AND JOSEPH A. LUHAN, M.D.†

Shock therapy introduced by Sikel<sup>1</sup> and Meduna<sup>2</sup> and modified by Cerletti and Bini<sup>3</sup> has become an established method of therapy in psychiatric disorders. The manner in which improvement or recovery is brought about by the various shock therapies is a moot question, it would seem from experimental work carried out by various investigators that reversible metabolic alterations of a temporary character are induced in the central nervous system and these effects, when repeated, in some manner bring about alterations in structure-function relationship resulting in clinical improvement of the behavior disturbance called mental disease.

To many physicians uninitiated in its use shock therapy seems to be an exceptionally formidable procedure and its application confined within institutions devoted solely to the treatment of mental illness. The possibility of carrying out this treatment on an extramural basis came to our attention when several of our patients who were receiving treatment in a hospital for mental illness were required to leave for various reasons before their courses of treatment were completed. Since their improvement at this stage had not reached a satisfactory level, we were emboldened to attempt completion of treatment on an outpatient basis as an experimental venture. Our results were satisfactory and encouraging and prompted us to establish an outpatient facility for electroshock therapy at Loretto Hospital a small general hospital affiliated with the Loyola University School of Medicine.

At first some difficulty was encountered in deciding what type of psychiatric disorder would be amenable to this therapy on an outpatient basis. Experience has shown that this procedure is particularly applicable in those cases of psychiatric disorder not accompanied by too blatant a behavior disturbance such as many depressive states of varied etiology, certain varieties of acute schizophrenic reactions,

---

From the Department of Neurology and Psychiatry, Loyola University School of Medicine, Chicago.

\* Associate Professor and Chairman of the Department of Neurology and Psychiatry, Loyola University School of Medicine.

† Associate Clinical Professor of Neurology and Psychiatry, Loyola University School of Medicine.

severe psychoneuroses, and the quasi-organic cases sometimes classified as psychosis with cerebral arteriosclerosis, accompanied by depression without significant memory loss or intellectual impairment.

Many of these patients could not be treated if inpatient hospitalization for the purpose of administration of shock therapy were insisted upon, mainly for economic reasons but also because of the objectionable connotation of confinement in a psychiatric section of a general hospital or in an institution devoted solely to the care of the mentally ill. One can frequently obtain much more cooperation from the patient himself if treatment is offered and he is allowed to remain at home or in his usual environment. In many patients, removal to a psychiatric hospital brings about a major adjustment difficulty which frequently aggravates the psychiatric disorder. As one of our depressed patients remarked, "I'm not nuts yet. Doctor, don't send me to a crazy hospital!" It would seem that the wider use of outpatient therapy would serve to relieve the present overcrowding in mental hospitals and the psychiatric facilities in general hospitals, and make therapy more easily available to many neglected borderline cases of mental illness sadly in need of help.

It has also been our experience that the existence of the outpatient facility in a general hospital oftentimes makes possible the satisfactory treatment of patients who exhibit a fairly acute behavior disturbance requiring hospitalization for a few days but responding to shock therapy with rapid amelioration of the acute symptoms, permitting the remainder of the treatment to be continued on an outpatient basis. This allows most general hospitals to serve as emergency psychiatric facilities provided that the directors or administrative officers are willing to cooperate in the minor adjustments necessary for the establishment of an outpatient shock therapy facility.

In our opinion, electroshock is preferable to the other two methods of shock therapy for use as an outpatient procedure. Insulin treatment is a much more cumbersome and dangerous method, requiring many hours per treatment and a selectively trained personnel to administer it. Metrazol, while simpler to use than insulin, must be introduced intravenously in varying dosage so that the desired convulsive effects are difficult to achieve, but the chief objection to its use is the terrifying apprehension developed in the patient by its administration so that cooperation for subsequent treatment becomes difficult or impossible to obtain. Frequently the resulting seizure is more severe and traumatizing than that obtained with electroshock.

## TECHNIC AND APPARATUS

At the Loretto Hospital suitable arrangements were made in the physiotherapy department because convenient booths, enclosing treatment tables, and the necessary personnel were available. Help is frequently obtained from the general nursing and technician personnel of the hospital.

In our treatment plan we insist that a responsible friend or relative accompany the patient to the hospital. This serves a dual purpose: the relative can watch the patient during the post-treatment arousal period, thus relieving hospital personnel of this duty, and he acts as a protective companion for the perhaps dazed and slightly amnesic patient on his return home.

Preparation of the patient includes the interdiction of food or drink for a period of about four hours before treatment is given. The urinary bladder should be emptied just prior to treatment. These precautions prevent the possible aspiration of stomach contents in an unconscious patient, and soiling with urine which otherwise is occasionally encountered.

Permission for the treatment should be obtained in writing on a provided form from the patient or close relative before treatment is instituted. A general physical and neurologic examination is made of each patient and if any questionable cardiac abnormality exists an electrocardiogram is obtained before treatment is started. Further diagnostic studies, such as x-ray of the chest in suspected pulmonary disease, roentgenographic examination of the spine (in instances of suspected osteoarthritis or old spinal injury) or of the long bones (when severe osteoporosis is feared) may be indicated before treatment is begun.

The machine used is an Offner electroshock therapy apparatus which delivers a sine wave alternating 60 cycle current whose duration and strength may be varied by an electronic device. With this type of apparatus the treatment current intensity which is more important than the voltage, may be predetermined by the passage of a high frequency testing current which is not felt by the patient.<sup>4</sup>

The beds provided are ordinary wooden examining tables with overlying pads. Sandbags are placed underneath the patient to bring about hyperextension of the dorsal spine and tend to prevent the occurrence of vertebral fracture. However a surgical bed which can be broken or adjusted may be used. In such a bed the patient is placed with his head at the foot and the appliance ordinarily employed to flex the knees can be used in the place of a sandbag to hyperextend the dorsal spine.<sup>5</sup>

With the Offner apparatus the electrodes are attached to a perfo-

rated rubber band which encircles the head and holds them in a fronto-temporal position. An electrode jelly is applied to the skin and small cotton pads moistened with saline solution are interposed between the electrodes and skin surface. We have not found it necessary for the assistants to wear rubber gloves.

The patient is held by four assistants (Fig. 37). One of these, especially trained, inserts and maintains in place a gauze-covered rubber mouth protector, supports the jaw to prevent dislocation of the mandible, and supervises the restraint applied by the other three assistants. One assistant restrains the lower extremities while the other two



Fig. 37—Position of patient and assistants during treatment

exert pressure upon each shoulder girdle and upper extremity. The rubber mouth protector is simply a segment of rubber hose or a rubber door stop covered with gauze, and is used to prevent injury to the tongue and other soft tissues of the mouth during the biting movements which occur as part of the convulsive seizure. Removable artificial dentures are taken out of the mouth as a preliminary to the treatment. As preparations are being made the current is turned on in the machine to allow the tubes to become warm. The connecting terminal plugs from the machine are then inserted into the electrodes and the instrument is adjusted to deliver the predetermined current. In our experience, generalized convulsions (so-called grand mal seiz-

ures) can usually be produced with a current of 350 to 450 ma. and a time interval of 0.5 second. Occasionally in heavily sedated individuals, those with deep depression or older persons, the milli-ampereage may have to be increased as well as the time. In our experience at Loreto Hospital thus far the most refractory patient has responded with generalized convulsions to a dose of 600 ma. for 0.7 second. In 75 per cent of our individual treatments, convulsions were achieved on the first attempt with 400 to 450 ma. acting for a period of 0.5 second.

It has been the experience of all workers in this field that petit mal-like responses (momentary loss of consciousness without convulsive movements) are therapeutically inefficient. Consequently, when a grand mal seizure fails to appear with a given dose, a second shock of higher milli-ampereage or longer time, or both, is given after respirations have returned to a normal rhythm, usually within three minutes. If a convulsive response is not obtained in three trials, we believe that further treatment attempts should be deferred for twenty-four hours. Once the convulsive threshold dose for a given patient is determined, grand mal-like responses may be obtained in subsequent treatments administered to that patient in most instances with this same amount of current.

The electrically induced grand mal-like attack resembles an idiopathic epileptic seizure in many of its dramatic aspects.<sup>6</sup> When the circuit is closed instantaneous loss of consciousness ensues, followed almost at once or in a few seconds by the convulsive phenomena which are usually more severe than in the epileptic seizure and follow a motor pattern somewhat different from that seen in the usual case of idiopathic grand mal seizure. From a practical standpoint, however, one must bear in mind that the initial manifestation of the electrically induced fit is unusually severe. The pupils become dilated and do not react to light during and for some time after the convulsion, and the eyeballs usually deviate conjugately upwards or to one side. After a temporary pallor the face becomes flushed and, as the period of apnea may be prolonged for many seconds, considerable cyanosis can develop. Retrograde amnesia for the convulsion regularly occurs.

The assistants must be on the alert to restrain the patient adequately during this startling, lightning-like initial lunge because at this time injuries most frequently occur. The assistants should be prepared for the suddenness and violence of this reaction and cautioned to exert full restraint in anticipation of circuit closure. Occasionally the onset of clonic convulsions is delayed for as long as fifteen seconds after the initial loss of consciousness ("delayed grand mal reaction") so

that restraining measures should not be relaxed if an immediate convulsion does not ensue with closure of the electrical circuit

As soon as convulsive movements cease the patient is quickly turned on his right side and a pillow placed beneath the head for support. This position is maintained until regular respiration reappears and marked salivation no longer occurs, usually in three to five minutes

As consciousness is being regained, acute restlessness with clouding of consciousness occurs in a considerable proportion of cases and rarely amounts to an acute furor reaction. For this reason we deem it advisable to apply restraining straps or bands across the chest and over the lower extremities above the knees as soon as the patient is replaced on his back. This can be done by means of folded sheets which are passed beneath the table around the patient and tied

Depending on how rapidly and completely consciousness is regained, the patient is allowed to go home with his companion within one-half to one and a-half hours after the treatment. Both the patient and his companion are advised that he should return home to rest for the remainder of the day and, if headache occurs, to take 5 or 10 grains of aspirin

Treatments are ordinarily given three times a week. Before treatment is begun the relatives are informed that an increasing degree of memory disturbance may and probably will supervene as therapy is continued. They are reassured that this is a temporary disability, probably of therapeutic value, and will subside within a comparatively short time, usually within three to four weeks of termination of treatment. Soreness of the limbs and back is a frequent sequel of treatment, but this is ordinarily of no serious significance and has been produced by muscular and soft tissue strain

#### CONTRAINDICATIONS

The usual type of patient selected for treatment from a psychiatric standpoint was outlined above. However, in spite of these well marked psychiatric indications, certain accompanying disabilities may contraindicate this type of treatment or its use on an outpatient basis. As a contraindication to this form of therapy certain somatic disturbances assume paramount importance: acute febrile illness, advanced age, severe cardiovascular disease, bone and joint disorders predisposing to fracture or which would be aggravated by violent muscular movement, and latent tuberculosis which experience with related metrazol therapy shows may be stirred into activity

In spite of the seeming rigors of the treatment, in our experience many individuals with evidence of a moderate degree of cardiovas-

cular disease may be safely and beneficially treated by this method. In fact, we have treated some patients with advanced cardiovascular disease with striking benefit, especially when the psychotic manifestations seemed to be aggravating the physical disability. To illustrate this point the following case history is presented.

Mr. W. S., a white male 54 years of age, a professor of engineering in a technical college, had been under care for a year and a half for cardiovascular disease accompanied by fatigue, anorexia, headaches and an inability to carry on efficiently at his usual work. Three months before admission for electroshock therapy he went to Florida for a "rest." Here he found the situation not conducive to rest and attempted to return home. Transportation facilities were overloaded and he was forced to wait six weeks before suitable train accommodations could be obtained. During this period of delay the patient became increasingly uneasy and restless, and said that he and his wife would never get home. He felt that he was being watched by everyone and emanated a disagreeable odor because of the dissolution of his internal organs caused by excessive cigarette smoking. Upon arriving home these symptoms became more severe. He feared to leave the house, saying the neighbors would shoot him since they felt he was a neighborhood menace.

Examination revealed an emaciated male appearing older than 54 years. Palpable evidence of arteriosclerosis was present in the accessible vessels. There was also noted a vascular hypertension of 230/100 with moderate cardiac enlargement and electrocardiographic findings of coronary sclerosis with considerable myocardial damage and probable old infarction. The patient was markedly agitated, slept little and ate poorly, and continuously voiced the delusional ideas mentioned above. Electroshock therapy was deferred for about a week because of the seemingly great risk involved, and during this period the blood pressure remained at a high level (225/90 to 250/115). After a conference with his wife and a close friend, both of whom felt something must be done to forestall a state of exhaustion which seemed imminent, treatment was begun.

A grand mal seizure was obtained with 450 ma at 0.5 second. Respirations began promptly and after a temporary period of irregularity lasting three or four minutes, cardiac action resumed a normal rhythm. Blood pressure reading immediately after muscular movement subsided was over 300 systolic, which was the highest reading obtainable with the sphygmomanometer, diastolic pressure was 185.

Treatment was continued three times weekly for a series of seven treatments. At this point all psychiatric symptoms had disappeared and the patient resumed his former normal personality pattern. He has now been free from symptoms of his mental disorder for five months.



that restraining measures should not be relaxed if an immediate convulsion does not ensue with closure of the electrical circuit

As soon as convulsive movements cease the patient is quickly turned on his right side and a pillow placed beneath the head for support. This position is maintained until regular respiration reappears and marked salivation no longer occurs, usually in three to five minutes.

As consciousness is being regained, acute restlessness with clouding of consciousness occurs in a considerable proportion of cases and rarely amounts to an acute furor reaction. For this reason we deem it advisable to apply restraining straps or bands across the chest and over the lower extremities above the knees as soon as the patient is replaced on his back. This can be done by means of folded sheets which are passed beneath the table around the patient and tied.

Depending on how rapidly and completely consciousness is regained, the patient is allowed to go home with his companion within one-half to one and a-half hours after the treatment. Both the patient and his companion are advised that he should return home to rest for the remainder of the day and, if headache occurs, to take 5 or 10 grains of aspirin.

Treatments are ordinarily given three times a week. Before treatment is begun the relatives are informed that an increasing degree of memory disturbance may and probably will supervene as therapy is continued. They are reassured that this is a temporary disability, probably of therapeutic value, and will subside within a comparatively short time, usually within three to four weeks of termination of treatment. Soreness of the limbs and back is a frequent sequel of treatment, but this is ordinarily of no serious significance and has been produced by muscular and soft tissue strain.

### CONTRAINDICATIONS

The usual type of patient selected for treatment from a psychiatric standpoint was outlined above. However, in spite of these well marked psychiatric indications, certain accompanying disabilities may contraindicate this type of treatment or its use on an outpatient basis. As a contraindication to this form of therapy certain somatic disturbances assume paramount importance: acute febrile illness, advanced age, severe cardiovascular disease, bone and joint disorders predisposing to fracture or which would be aggravated by violent muscular movement, and latent tuberculosis which experience with related metrazol therapy shows may be stirred into activity.

In spite of the seeming rigors of the treatment, in our experience many individuals with evidence of a moderate degree of cardiovas

cular disease may be safely and beneficially treated by this method. In fact, we have treated some patients with advanced cardiovascular disease with striking benefit, especially when the psychotic manifestations seemed to be aggravating the physical disability. To illustrate this point the following case history is presented.

Mr. W. S., a white male 54 years of age, a professor of engineering in a technical college, had been under care for a year and a half for cardiovascular disease accompanied by fatigue, anorexia, headaches and an inability to carry on efficiently at his usual work. Three months before admission for electroshock therapy he went to Florida for a "rest." Here he found the situation not conducive to rest and attempted to return home. Transportation facilities were overloaded and he was forced to wait six weeks before suitable train accommodations could be obtained. During this period of delay the patient became increasingly uneasy and restless, and said that he and his wife would never get home. He felt that he was being watched by everyone and emanated a disagreeable odor because of the dissolution of his internal organs caused by excessive cigarette smoking. Upon arriving home these symptoms became more severe. He feared to leave the house, saying the neighbors would shoot him since they felt he was a neighborhood menace.

Examination revealed an emaciated male appearing older than 54 years. Palpable evidence of arteriosclerosis was present in the accessible vessels. There was also noted a vascular hypertension of 230/100 with moderate cardiac enlargement and electrocardiographic findings of coronary sclerosis with considerable myocardial damage and probable old infarction. The patient was markedly agitated, slept little and ate poorly, and continuously voiced the delusional ideas mentioned above. Electroshock therapy was deferred for about a week because of the seemingly great risk involved, and during this period the blood pressure remained at a high level (225/90 to 250/115). After a conference with his wife and a close friend, both of whom felt something must be done to forestall a state of exhaustion which seemed imminent, treatment was begun.

A grand mal seizure was obtained with 450 ma. at 0.5 second. Respirations began promptly and after a temporary period of irregularity lasting three or four minutes, cardiac action resumed a normal rhythm. Blood pressure reading immediately after muscular movement subsided was over 300 systolic, which was the highest reading obtainable with the sphygmomanometer, diastolic pressure was 185.

Treatment was continued three times weekly for a series of seven treatments. At this point all psychiatric symptoms had disappeared and the patient resumed his former normal personality pattern. He has now been free from symptoms of his mental disorder for five months.

The psychiatric contraindications include behavior disturbances of such intensity that institutionalization is required. Depressed patients with marked suicidal tendencies should not be trusted to the inexperienced supervision of relatives and friends and should, therefore, not be treated as outpatients. Organic brain disease such as general paresis, brain tumor, Huntington's chorea, parkinsonian states productive of behavior disturbances, senile dementia, Alzheimer's disease, and so forth, are unresponsive and treatment by this method is often dangerous.<sup>7</sup> Chronic, deteriorated schizophrenics rarely respond to treatment, therefore, while no contraindication exists, neither is there an indication for treatment. Occasionally when a patient with chronic schizophrenia who is able to remain at home under the supervision of relatives becomes acutely yet mildly disturbed, the acute behavior disturbance may be ameliorated by a course of shock therapy.

#### DANGERS AND COMPLICATIONS

The dangers and complications of indiscriminate electroshock therapy are considerable. Fractures occurred frequently with the use of metrazol, less often with electroshock, but in our experience are not a prohibitive hazard when suitable precautions are taken. Before hyperextension of the spine and adequate manual restraint were routinely employed, the incidence of fractures with metrazol convulsive therapy was high, with 43 per cent of one series of patients<sup>8</sup> developing single or multiple fractures of the bodies of the thoracic vertebrae. In later reports, fractures of other bones (humerus, scapula, femur, mandible) were described. With electroshock treatment given under similar conditions as metrazol, the proportion of fractures encountered was significantly smaller. Vertebral fractures complicating electroshock therapy can be largely eliminated by the use of hyperextension of the spine and proper restraint. Worthing and Kalinowsky<sup>9</sup> found that re-examination of eight patients with severe multiple spinal fractures incurred two years previously disclosed no orthopedic or neurologic evidence of progressive pathology, and expressed the opinion that fractures are no contraindication against shock treatment since they can largely be avoided and, if they do occur, have no clinical importance. We have not searched for vertebral fractures with the x-ray, should they occur, as in the past with the use of metrazol, little disability is caused and no special treatment is required. Considerable backache may develop after treatment on the basis of soft tissue strains without fracture. In our outpatient experience we have encountered no fractures of long bones. On several occasions

dislocation of the mandible occurred which was reduced before consciousness was regained and after the convulsion had ceased.

In the attempt to prevent the occurrence of fractures by "softening" the convulsion, *curare* was introduced by Bennett,<sup>10</sup> first in conjunction with metrazol and later with electrically induced convulsions. Curarization is not without danger, and the use of *curare* (Intocostin) in conjunction with electroshock is not advised unless the physician stands ready to combat prolonged apnea and suffocation by means of artificial respiration, the administration of prostigmine as an antidote and the insertion of an airway. We had not encountered any serious reactions with its occasional use on inpatients until two of four extramural patients treated with *curare* at Loretto Hospital developed alarming apnea, cyanosis and obstructive dyspnea. In one of these patients consciousness had already returned when the airway had to be inserted, and the patient refused further treatment because of recollection of this terrifying experience. We speculated that another indication for the use of *curare* might be found in hypertensive subjects to prevent or diminish severe transient rise of blood pressure occurring with the induced convulsion, but experience did not bear this out. Woolley<sup>11</sup> has shown that marked variations in blood pressure occur, often with violent rises in hypertensive subjects, in *curare* protected metrazol and electric shock. We feel, therefore, that *curare* should not be used in conjunction with outpatient electroshock treatment.

Fatalities associated with electroshock probably occur at the rate of about one in 1000 cases.<sup>12</sup> A number of these deaths took place when *curare* was used. In most instances death is caused by circulatory failure, acute cardiac dilatation in a previously diseased heart may result from the tremendous muscular exertion of the convulsion or circulatory failure may occur without obvious heart disease from disturbance of cardioregulatory and vasomotor centers. In our personal inpatient and outpatient experience with electroshock we have thus far not encountered a fatality.

In our experience no significant aggravation of the mental illness has taken place as the result of treatment. Each patient has exhibited a temporary memory disturbance, which may approach mild confusion as treatment progresses. If relatives and associates are forewarned to expect these symptoms much apprehension and anxiety is allayed. Occasionally severe transient excitement may follow treatment. This is a disturbing complication because of the pandemonium created and the possibility of injury to patient or personnel. In such patients it is our practice to terminate outpatient treatment at once.

We do not recommend electroshock therapy as a routine office procedure, in spite of the reported experiences of others<sup>13</sup> However, in certain so-called office clinics the facilities available may approach a hospital environment and be readily adaptable to the procedure.

In our experience, psychotherapy beyond that of instruction and simple reassurance seemingly has played no rôle It is possible that more subtle psychotherapeutic elements, such as the dramatics of the treatment, physician-patient relationship or other intangibles, may be operative We feel that formal and intensive psychotherapy during treatment is almost precluded because of the rapidly developing amnesia which accompanies this mode of therapy In this series we have avoided all psychotherapeutic efforts in order to evaluate the effects of electroshock treatment per se

#### RESULTS IN SEVENTY-FIVE CASES

This report does not attempt to evaluate the general results of electroshock therapy This has been and continues to be the subject of a number of studies<sup>14</sup> based on larger groups of patients We have given about 600 individual treatments during the past eleven months to seventy-five outpatients at Loretto Hospital The ages of these patients ranged from 16 to 68, with a median age of about 35 years The ratio of women to men was almost two to one Sixty-five patients have either completed their course of treatment or are no longer under treatment Of these, four received only one treatment and four more, only two Omitting these cases, the remaining fifty-seven patients received an average of seven treatments apiece The largest number of treatments administered in any one case was nineteen The period of observation since cessation of treatment varied from two to eleven months, and therefore it is too early to evaluate long term results In the fifty-seven cases the diagnosis and immediate results were as follows

Involucional depressions and psychoses, 17 cases, results, 13 good, 4 fair

Reactive depressions, 8 cases, results, 6 good, 1 fair, 1 poor

Manic-depressive depressions, 4 cases, results, 3 good, 1 fair

Marked psychoneuroses, usually with depressive features, 13 cases, results, 3 good, 8 fair, 2 poor

Schizophrenic psychoses and reactions, 12 cases, results, 3 good, 6 fair, 3 poor

Cerebral arteriosclerosis with depression, 2 cases, results, both good

Psychosis with mental deficiency, 1 case, result, good

Thus in depressive states particularly involutional, manic-depressive and so called reactive depressions, good immediate results were obtained in over three-quarters of the patients treated, whereas in psychoneuroses, particularly with some depressive features but in which psychosomatic complaints and phobias dominated the picture, and in schizophrenic reactions and psychoses, only about a fourth of the patients underwent marked improvement following treatment. No benefit whatsoever accrued from this therapy in about 11 per cent of the whole group of patients.

The case history previously cited illustrates an immediate therapeutic result classified as "good." As an example of a "fair" result the following case may be cited.

A 37 year old married woman who previously made a satisfactory social adjustment, gradually developed symptoms of mental illness, becoming overt two months before she came under psychiatric care. She had gone to work in a "defense" factory ostensibly to defray the expense of a college education for her 17½ year old son. After some months she became infatuated with the foreman at her place of work, this was clearly an autistic love affair, and took on serious proportions only after the son, to whom she was strongly attached entered the Army and shortly thereafter became engaged to be married without his mother's knowledge or consent. In effect the boy had jilted his mother for a sweetheart after the former had made sacrifices to enable him to become well educated and make a mark in the world. The patient spoke freely of her infatuation for this foreman and entertained the idea that he reciprocated her affections but was afraid to admit it. As a result of conflict over this infatuation she left her job two months prior to treatment, expressed increasing dislike for her husband, and finally left her home to stay with a relative.

She related to the examiner how for some months she had been watched and followed by mysterious persons who would take flash-light pictures of her, since she heard the click of the camera and saw the bursts of light. Her husband, a janitor, appeared very much devoted to his wife but apparently had not been aware that she was suffering from a serious mental illness.

It was explained to the patient that she had undergone such nervous shocks that she was in no condition to make major decisions concerning separation or divorce from her husband and was finally prevailed upon to enter Loretto Hospital as an inpatient for a course of shock treatment. The diagnosis was paranoid schizophrenic psychosis. She remained in the hospital for a week receiving four treatments, and continued treatment as an outpatient for three more treatments. Her condition improved, she became reconciled with her husband, has resumed her former household responsibilities, gave approval for her

son's marriage, and no longer felt that she was being followed and photographed. She no longer spoke of her infatuation for the foreman. Her husband considers her well, but the patient has no insight into her behavior and shows some affective leveling. She has continued to make a satisfactory adjustment for the past ten months.

### SUMMARY

We have discussed the evolution and practical operation of an outpatient electroshock facility in a small general hospital. The advantages of such outpatient treatment are mainly economic, and make therapy available to many neglected borderline cases of mental illness. The selection of patients for treatment, the dangers and complications of this method and the results in a preliminary series of cases are reported.

### BIBLIOGRAPHY

- 1 Sakel, M. Schizophreniebehandlung mittels Insulinhypoglykämie. *Wien med Wchnschr.*, 84 1211, 1934
- 2 Meduna, Ladislaus J. Versuche über die biologische Beeinflussung des Ablaufes der Schizophrenie, Kamfor und Cardiazolkrämpfe. *Ztschr f d. ges Neurol u Psychiat.*, 152 235, 1935
- 3 Cerletti and Bini. "L'elettroshock." *Arch gen di neurol., psichiatria e psicoanalisi*, 19 266, 1938, abstr in *Zentralbl f d. ges Neurol u Psychiat.*, 93 486, 1939
- 4 Offner, Franklin. Electrical Properties of Tissues in Shock Therapy. *Proc Soc Exper Biol & Med.*, 49 571, 1942
- 5 Friedman, Emerich, Brett, A. Leo and Vogt, Edward C. Compressions of the Vertebral Bodies during Convulsive Therapy. *New Eng J Med* 222 704 (April 25) 1940
- 6 Gonda, Victor E. Treatment of Mental Disorders with Electrically Induced Convulsions. *Dis of Nervous System*, 42 84 (March) 1941
- 7 Heilbrunn, Gert and Feldman, Paul. Electric Shock Treatment in General Paresis. *Am J Psychiat.*, 99 702 (March) 1943
- 8 Polatin, Phillip, Friedman, Murray, M., Harris, Meyer M. and Horwitz William A. Vertebral Fractures Produced by Metrazol-Induced Convulsions in the Treatment of Psychiatric Disorders. *J.A.M.A.*, 112 1684 (April 29) 1939
- 9 Worthing, Harry J. and Kalinowsky, Lothar B. The Question of Vertebral Fractures in Convulsive Therapy and in Epilepsy. *Am J Psychiat.*, 98 533 (Jan.) 1942
- 10 Bennett, A. E. Preventing Traumatic Complications in Convulsive Shock Therapy by Curare. *J A M A.*, 114 322 (Jan 27) 1940
- 11 Woolley, Lawrence F. Immediate Circulatory and Respiratory Effects of Convulsive Shock (Curare Protected Metrazol and Electric Shock). *J Nerv & Ment Dis.*, 100 1 (July) 1944
- 12 Jerter, Walter W. Fatal Circulatory Failure Caused by Electric Shock Therapy. *Arch Neur & Psych.*, 51 557 (June) 1944
- 13 Wender, Louis, Balser, Benjamin H. and Beres, David. Extramural Shock Therapy. *Am J Psychiat.*, 99 712 (March) 1943
- 14 (a) Neyman, Clarence A., Urse, V. G., Madden, John J. and Countryman, M. Alden. Electric Shock Therapy in the Treatment of Schizophrenia.

Manic-depressive Psychoses and Chronic Alcoholism *J Nerv & Ment Dis.*, 98:618 (Dec ) 1943

- (b) Impastato, David J. and Almansi, Renato J. A Study of Over Two Thousand Cases of Electront Treated Patients *New York State J Med.*, 43:2057 (Nov 1) 1943
- (c) Malzberg, Benjamin. The Outcome of Electric Shock Therapy in the New York Civil State Hospitals *Psychiatric Quart.*, 17:154 (Jan ) 1943
- (d) Kalinowsky, Lothar B. and Worthing, Harry J.. Results with Electric Convulsive Therapy in 200 Cases of Schizophrenia *Psychiatric Quart.*, 17:144 (Jan ) 1943
- (e) Pacella, B. L. and Barrera, S. E. Follow-up Study of a Series of Patients Treated by Electrically Induced Convulsions and by Metrazol Convulsions. *Am J Psychiat.*, 99:513 (Jan ) 1943



# INSOMNIA

MEYER SOLOMON, M D \*

THIS discussion will be limited to insomnia in adults, with special emphasis on ambulatory office patients rather than home-confined, hospital or sanitarium patients

Although etymologically insomnia, or sleeplessness, means lack of sleep from any cause or causes, ordinarily it is used synonymously with hypsomnia or lessening of the duration or depth of sleep, or both, acute or chronic, from any cause or combination of causes, psychologic or nonpsychologic. Since the depth and duration of sleep vary considerably from one individual to another and from one season to another, and since, unless the behavior is such as to attract the attention of or to annoy others, there is often no good objective criterion of insomnia, it is usually, insofar as ambulatory office patients are concerned, a subjective complaint unless supported by confirmatory observation of members of the family or others

The complainant's story and interpretation may or may not be correct, since it may vary according to his well-being and how much significance he attaches to getting a certain number of hours of sleep of a quality satisfactory to himself. As Klingman,<sup>1</sup> quoted by Kleitman,<sup>2</sup> has so neatly put it "Those who sleep eight hours and believe that they need ten consider themselves to be suffering just as much from insomnia as others who cannot get more than four or five hours of sleep but who would be satisfied with six or seven." It should be added, nevertheless, that under certain circumstances some persons who get ten hours as their average sleep are not in optimum condition on two hours less. But such decrease in their preferred amount of sleep can usually be corrected by reorganizing their daily routine or conditions of living by establishing an earlier hour of retiring, correcting the physical arrangement in the bedroom, and investigating such causes of morning awakening as noise or light.

It is therefore important to check the patient's complaint of insomnia carefully, with full details as given by the patient and, if possible, by others in the home, before accepting at its face value the truth of the general complaint as given by the patient. For example,

---

From the Department of Nervous and Mental Diseases, Northwestern University Medical School, Chicago

\* Associate in Nervous and Mental Diseases, Northwestern University Medical School, Chairman, Department of Neuropsychiatry, Mount Sinai Hospital

a patient complained to me that, among other annoyances she had suffered from poor sleep for two years past. On careful inquiry it was learned that this amounted to nothing more than partially awakening in the middle of the night for a few minutes or so and immediately dropping off to sleep again and sleeping soundly until about 8 o'clock in the morning. Furthermore, she had lost no weight and had none of the other clinical effects of real sleeplessness over a two year period.

### CLASSIFICATION OF INSOMNIA

Insomnia is unquestionably one of the most common complaints in medical practice. Although there are many classifications of the condition, such as age, degree of completeness, clinical diagnosis, and whether acute or chronic, I shall refer here in particular to classification according to cause and to time of incidence.

Based on the time of incidence there are three types of insomnia (1) Difficulty or delay in falling asleep, known as *initial* or *predormitional insomnia*. This is the most common type and results especially from habit, fear, worry and anxiety states, with the ability to sleep late in the morning. Laird<sup>7</sup> goes so far as to claim that it occurs in three fourths of the population. (2) Intermittent, broken, restless sleep, which varies almost directly with age, and Laird<sup>7</sup> believes that it occurs in about 40 per cent of adult men. This type of insomnia is commonly associated with unpleasant dreams and nightmares, and in middle-aged persons is frequently accompanied by digestive disturbances. (3) Early morning awakening, so-called *terminal insomnia*, with difficulty in returning to sleep. This is normal with advancing age, is common in arteriosclerosis and hypertension and, I agree with Pollock,<sup>8</sup> Muncie<sup>9</sup> and many others, is especially present in mental depression.

It has been found that most people wake up spontaneously during the second half of the night but fall asleep again, and that when one has had "enough" sleep, one awakens more and more frequently and finds it more and more difficult to fall asleep again until finally one remains awake.<sup>2</sup> When this final stage is reached by 3 or 4 or 5 o'clock in the morning instead of the usual hour of awakening (6 or 7 or 8 o'clock or so), the condition is called terminal insomnia. When this occurs in elderly persons, who ordinarily need less sleep than formerly but who go to bed at the usual if not an earlier hour and are worried if they do not sleep to as late an hour as previously or as late as younger people do, one need have no concern. Also, it is not merely a question of how early one awakens but how early one re-

tures, how many hours of sleep one has had and how light or heavy a daily program one follows

Combinations of the above three types of insomnia may occur. Occasionally there is a reversal of the sleep rhythm with wakefulness by night and sleep by day, as in some cases of epidemic encephalitis and in cerebral arteriosclerosis with other manifestations of senility.

### CAUSES OF INSOMNIA

Insomnia is a symptom of some underlying cause or causes. There are three main groups of causes, as follows:

(1) *Purely external*, such as extremes of heat or cold, light (especially early morning sun), noise (especially early morning traffic), uncomfortable bedding, crowding, and so forth.

(2) *Physical diseases and toxic causes*. This covers a large number of conditions, including pain or severe discomfort from injury or disease of any kind, organic disease not especially accompanied by pain, as in tuberculosis, arteriosclerosis, thyrotoxicosis, heart disease and hypertension, organic brain disease, tinnitus aurium, or post-traumatic, or from arthritis, neuritis and the like, cerebral excitement from endogenous toxic states such as infection or uremia, as well as from exogenous toxins such as the excessive use of coffee, tea or alcohol especially in the latter part of the day, gastro-intestinal disturbances with discomfort from dyspepsia, indiscretions in diet, hunger, hypoglycemia, and so forth.

(3) *Psychological causes*. These are the most common causes of insomnia and comprise the whole range of mental and emotional factors, the psychoneuroses (fatigue or neurasthenic, anxiety, hysterical and obsessive-compulsive states) and psychoses (especially depressed, excited, confusional and schizophrenic states), worry about and especially fear of insomnia, of the possibly serious effects of sleeplessness, of insanity and of incurability. Insomnia which is not traceable to physical disease or to some definite physiological or external origin, is most apt to be associated with anxiety about something and it is our job to find out just what that something is.

It is clear that insomnia is always a definite indication that something about the patient needs investigation since it may be the end product of a multitude of possible causes and, like cough or pain or dyspnea, is only a symptom. Difficulty in sleeping dependent upon residual excitement from the day is not uncommon in sensitive, excitable, worried individuals. Some such individuals have a certain degree of recurrent insomnia of many years' duration.

Psychogenic insomnia with sleeplessness as the only complaint at

the original consultation is often complex and requires careful study, diagnosis and management. In other instances it is simple in origin and management from the very beginning.

It will not be possible to discuss the characteristics and treatment of insomnia in special clinical conditions such as delirious, excited and similar states. This aspect will be found in the various clinical texts on psychiatry or psychological medicine.

#### CLINICAL EFFECTS OF LOSS OF SLEEP

For an authoritative discussion of sleep which, unfortunately, I have no space to present, I urge you to consult the very splendid book by Kleitman<sup>2</sup> on *Sleep and Wakefulness*. He conducted experiments on partial deprivation of sleep with continued muscular activity so that the effects were due partly to lack of sleep and partly to muscular fatigue. In his standard procedure there was a waking period of sixty-two to sixty-five hours of staying awake until late in the evening of the third day of sleeplessness. He himself remained awake on various occasions to 100 hours and with the aid of benzedrine sulfate as long as 180 hours. He found, in general, no deviations from the normal range in the vegetative functions (heart rate, blood pressure, body temperature, basal metabolism, appetite, composition of the blood and urine), while the red blood cells and hemoglobin percentage showed variable results but with no general tendency to oligocythemia.

In studying the effects on the nervous system, Kleitman employed two classes of tests with the following results: (1) Tests in which effort is not a determining factor (knee jerks, pupillary light response, cutaneous sensibility to faradic current, touch and pain, visual acuity, brain potentials, electrical skin resistance) showed, as with vegetative functions, no consistent variation for the group as a whole for all tests but one, namely, sensitiveness to pain, with cutaneous sensitivity to touch unchanged but to pain a progressive increase (lower thresholds). (2) Tests in which effort is a determining factor showed in general a decreased performance ability during the period of sleeplessness. Although mental and muscular performance in various tests can be maintained at normal levels if the tests are of short duration, sustained effort is impossible. The most outstanding and significant findings in all studies on lack of sleep were found to be increased sensitivity to pain, impairment of the disposition with hyperirritability and irascibility, a tendency to day-dreaming, hallucinations and other similar signs. All of these point to fatigue of higher levels of the cerebral cortex, which are in constant operation during the period of

wakefulness and are responsible for the critical analysis of incoming impulses and the establishment of adequate responses in the light of the person's or animal's experience Kleitman found in humans itching or slight burning sensitiveness of the eyelids, and mild mannered persons became ill tempered under continued efforts to keep them awake Thus, the sleepy individual can make a short lasting effort but cannot sustain it.

Many experiments have shown that animals die from lack of sleep <sup>3</sup> Menace's puppies after four to six days, Tarozzi's three dogs after nine, thirteen and seventeen days, although Pieron's twenty dogs were alive after from 30 to 505 hours and Okazaki's after fourteen to seventy-seven days, of Kleitman's twelve puppies kept awake from two to seven days two died without awakening after being permitted to sleep In experimental animals which died or were killed after a period of insomnia, various brain and other nervous system changes have been reported

Kleitman concludes <sup>4</sup> "From observations made on persons undergoing experimental insomnia it can be stated with assurance that no immediate untoward developments need be feared from the loss of a night's sleep, whether it be partial or complete Prolonged, continuous wakefulness, however, even if undergone voluntarily, may cause temporary mental deterioration"

Insomnia in clinical practice is a more complicated matter Here the patient is worried about his sleeplessness, he knows that it is not voluntary or merely experimental, and it may continue not merely for days but for weeks and months Varying with the cause, we commonly note increased fatigue, lack of concentration, deficiencies of memory, inability to perform effective mental work, impairment of muscular coordination (especially for more delicate movements), anorexia, irritability of temper, loss of weight, head and bodily paresthesias, restless and agitated pacing of the floor, and general physical and mental instability <sup>10</sup> Weight loss, especially in depressed patients, due to insomnia, anorexia and other factors, may be as much as 20 to 50 pounds

Craig<sup>11</sup> is right when he says "Some persons are much more intolerant of deficient sleep than are others, indeed, some individuals will become definitely insane within a few days if sleep is not obtained" Popov<sup>5</sup> reports such a case, with complete recovery after the patient was allowed to sleep

I also agree with Minogue<sup>12</sup> of Australia who found that insomnia from whatever cause led to rapid mental and physical exhaustion, usually with headaches, especially a "tight band around the head" as

if "the head were bursting" If long continued, the patients become desperate, restless, apprehensive, many are haunted by the fear of insanity, some may later become suicidal, especially if living alone, with no relatives or friends to console them, if too religious or if elderly Minogue quite correctly concludes "Suicide is the end result of a large number of factors, both physical and psychological. Whatever its cause, it is generally preceded by a period of insomnia with its concomitant symptoms and signs. It is imperative for us to realize the risk of suicide in such patients and also that the patient requires urgent and immediate treatment. If appropriate treatment is given, I am convinced that many a suicide can be prevented, a fact well known to all psychiatrists. But unless we, as a profession, realize that sleepless, depressed and worried patients are prone to suicide, and that such patients can be very successfully treated by modern psychiatric methods, there seems to be little hope of appreciably reducing the suicide rate in Australia." What is true of Australia is likewise true of the United States.

In considering the dangers of real insomnia, one must appreciate the possibility of a vicious circle with insomnia aggravating the nervous and mental condition, and vice versa. I have summarized<sup>13</sup> the situation briefly in a previous discussion in the following words: "It is not merely the direct results of lack of sleep but its indirect and psychological results which are of serious import. The patient's hours of wakefulness at night, with everyone else sleeping and all quiet, may seem to him very much longer than they in fact are. It is also during such periods at night that his rushing thoughts, emotionalism, anxiety, worries and fears take possession of him in more unrestrained fashion. Then come his worries over the real or imagined dangers of insomnia. Being more unstable because of insomnia, he is inclined the following day to be more in the grip of his anxieties and fears. His worry about the lack of sleep leads to an excessive interest in whether or not he will sleep well. He may have actual despair from his sleeplessness. Fear of the night, of insomnia and of bed time may become predominant. Fear of insanity may result from insomnia primarily or be exaggerated by it. Although insomnia is only one cause of the fear of insomnia in psychoneurotics (and psychotics) it is an important cause. Continued sleeplessness may lead to a feeling of lack of self-confidence and self-control."

In all cases of persistent, prolonged insomnia the patient should be studied carefully to determine whether or not a real mental depression is not the actual clinical condition present, and, if so, it should be treated as such, with, if severe enough and indicated, hospitaliza-

tion and so-called electroshock therapy, in selected cases estrogen therapy<sup>15 16</sup> in the female and androgen therapy<sup>17</sup> in the male have apparently been of value in true involutional melancholia

### GENERAL MANAGEMENT OF INSOMNIA

In all cases a careful sequential history of the onset and development to date is essential. This should include its degree, duration, effects, probable cause of onset, factors responsible for its continuation, and the patient's attitude toward his condition. His other complaints should be gone into sufficiently fully. Review the patient's daily program—his time of arising, routine of the day, hour of retiring, the amount and character of his sleep before and since the onset of his insomnia.

A personality estimate and determination of the mental condition, with decision as to the existence or absence of a psychoneurosis or psychosis and the approximate clinical diagnosis can usually be made during the first extended consultation.

Take the complaint of insomnia as seriously as you do (or should) any other symptom.

At the outset a full physical examination should be made with definite exclusion of obvious causes (such as pain, dyspnea, pruritus), diseases of the gastrointestinal, circulatory, respiratory or excretory systems, hypertension, organic neurologic diseases and alcoholic toxic states. Whatever laboratory tests are really necessary should not be omitted. By this time you should have a more definite opinion concerning the patient and his complaint.

Each case is an individual affair. No fixed rules can be laid down.

Unless the patient is willing to put himself under your care, to see you frequently enough and to permit proper study and supervision, it is better to give merely general advice, outline the situation and not prescribe hypnotics except for two or three nights and then not to be refilled. Explain your reasons to the patient.

All psychoneurotic patients with insomnia, except of the slightest degree, are much better sleeping alone. All clocks are generally best removed. A dark, quiet, properly ventilated room is desirable.

Each individual has his favorite, preferred choice of bedspring, mattress, bedding, pillow arrangement, ventilation and posture in bed. If there is increased blood pressure, have the patient try using no pillow.

If there is sensitiveness to cold, a warm bed—even with hot water bottles—is in order. If cold feet while in bed are a source of discomfort, help may be found in a hot foot bath at bedtime, or hot water

bag to the feet, being sure to avoid burns, or the patient may wear woolen socks to bed.

If the patient is hungry at bedtime, milk or warm soup with crackers a half hour before retiring should be soporific. If awakening occurs from hunger, a glass of milk and crackers may be taken at the time of awakening.

If there is overuse of coffee, tea or alcohol, reduce the amount consumed during the latter part of the day or after lunch, especially at or near bedtime. The effect of coffee and tea varies from one person to another.

If there is flatulent distention of the stomach or intestines, try one-half glass of water with 10 to 15 grains (0.65 to 1 gm.) of sodium bicarbonate at bedtime.

For disturbing symptoms in medical or surgical conditions, such as cough or dyspnea, relief as necessary is in order. Some patients are helped, others made worse, by a glass of hot whiskey or water, by reading, or by attempts at muscle relaxation at bedtime. Gentle massage, especially of the spinal muscles, just before the usual sleeping time is apt to be valuable, especially in neurasthenics and bed patients.

To exclude the early morning light, opaque window shades (dark green shades instead of or in addition to yellow, tan or white ones) should be drawn low at bedtime. For sleeping by day, the use of an opaque screen about two feet from the window is helpful. Avoid having the light fall directly on the head.

Sedative hydrotherapy may be employed in several ways: as prolonged (one quarter to one-half hour) warm (96° F.) bath, cold wet pack for three-quarters to one hour, or, in excited states, neutral tub baths for two or three hours or continuously, especially with an ice cap to the head. The last is always, and the second is usually, a hospital procedure.

Suggestion, assurance, diversion, distraction, release of anxiety and tension are occasionally of service as conditioning processes to induce sleep. Drinking or eating or even a warm bath, muscular relaxation, various psychological procedures such as listening to one's breathing, prayer, autosuggestion of Coué, naming categories following the alphabet, and so on.

If sleeplessness follows a period of unusually concentrated or prolonged mental work, a short vacation with plenty of rest and sleep should be advised, often at the onset, with the addition of mild hypnotic medication.

I know that many of the above suggestions cannot be carried out in certain patients owing to limitations of living quarters, hours of



employment and financial situation, but no symptom demands such varied therapeutics

As Kleitman<sup>6</sup> concludes "Insomnia, in the sense of hypsomnia, is nearly always traceable to some disturbing factor, capable of keeping the cortical centers, or the wakefulness center in the hypothalamus, directly in a state of prolonged activity. The therapeutics of insomnia consist in the removal of the disturbing factors and, if that fails, in the use of depressing drugs"

In the majority of cases no physical cause can be found for the insomnia and the patient needs a combination of a common sense exploration of his mental and emotional problems with psychological management, a survey of his daily program of activity, and the rational use of hypnotic drugs

#### PSYCHOLOGICAL ASPECTS AND PSYCHOTHERAPY

In considering psychogenic insomnia, emotional conflict is so important that its consideration is really an introduction to the problem of psychoneuroses and so-called functional psychoses. Thus, the management of the patient goes step by step with the treatment of the symptom of sleeplessness. This means an investigation of the patient's personal problems, his state of health, his daily program, domestic (marital and family), financial, occupational, social, recreational, sexual, religious, and ethical-moral adjustments

The attitude of the physician must very definitely be one which inspires confidence. The physician must have and show confidence in his own ability to help the patient recover and in the patient's ability to regain his equilibrium

In the treatment of a disease associated with insomnia, one must remember that in continued pain with prolonged insomnia, especially in unstable individuals, eventual psychoneurosis or even psychosis may result. In like manner organic disease of any sort may clear up and insomnia continue

Discuss the past anxieties which led to or the present anxieties which maintain the insomnia. With time, interest, sympathy, patience and understanding in the very first interview or the first few interviews, the patient will confess his anxieties, medical and nonmedical. Some can, others cannot, be settled by discussion. If you cannot remove the anxiety responsible for the sleeplessness, at least reassure the patient as much as possible. Use explanation, suggestion and readjustment of his daily program, attitudes and ambitions, as the case may be.

If intensive personality study is indicated, I do not favor adhering to any one school of psychological thought, Freudian or otherwise,

but study each patient individually, letting the quips fall where they may

I do not find any real basis to the current systems of dream interpretation and their supposed invariable importance and value in unearthing the causes of the disorder

Hypnosis is ordinarily of no, little or temporary value and it may not be possible to use it in sleeplessness in office patients

#### PHARMACOTHERAPY THE USE OF HYPNOTIC DRUGS

Owing to space limitation I shall confine my discussion to the pros and cons of using hypnotics in general and to technic and precautions in their use

The chemistry, characteristics, dosage and methods of administration of the various drugs can be found elsewhere, as in the presentations by Weiss,<sup>18</sup> Feiling,<sup>19</sup> Fantus,<sup>20</sup> Winans,<sup>21</sup> Darcum,<sup>22</sup> Diethelm,<sup>23</sup> Ross,<sup>24</sup> Crichton-Miller<sup>25</sup> and Gralfield.<sup>26</sup> For special attention to the barbituric acid group I refer you to Weiss<sup>18</sup> and the special report of the *Journal of the American Medical Association*<sup>27</sup> Goodman and Gilman<sup>28</sup> give a comprehensive discussion

**The Case For and Against the Use of Hypnotics**—Sleeplessness due to pain and other discomfort requires necessary symptomatic relief, even morphine or codeine. Hyoscine is used exclusively in selected cases in psychiatric hospital practice. Bromides are rarely effective in insomnia of real consequence. Chloral and paraldehyde, not used as frequently now as formerly, are in my opinion for hospital and sanitarium rather than home use in ambulatory office patients

By hypnotics I refer more particularly to the drugs of the barbituric acid group such as barbital, veronal, medinal, sodium amytal, ipral, nembutal, seconal, "delvinal" sodium and many others, and much less to the so-called sedative group, bromides, chloral, paraldehyde, but not at all to the so-called euphorotics (alcohol, opium, morphine, heroin, cocaine) I agree with others that with a change of dosage a so-called sedative may produce hypnosis or narcosis.

Surely there can be no scientific objection to the desirability or necessity of medication for actually disturbing symptoms of emotional origin, as for instance the temporary use of hypnotics for psychogenic insomnia while the patient is being studied and treated causatively. And yet there is a surprising disagreement in attitude and policy on this important clinical problem. This is especially so in the case of insomnia accompanying the psychoneuroses. As I<sup>18</sup> have said elsewhere, among the large number of psychotherapists and psychopathologists who are in direct opposition or do not openly advocate or even mention the occasional necessary use of hypnotics in the treat-

ment of insomnia in the psychoneuroses, I found such names as Du-bois, Janet, Freud, Jung, Adler, McDougall, Prince, Dejerine and Gauckler. Yet we find that Dejerine and Gauckler<sup>20</sup> admit that the patient with insomnia of phobic origin often clings to his fear of insomnia so strongly that the bad habits which he has formed are frequently kept up in spite of all psychotherapeutic efforts.

As a consequence of the many arguments against the use of hypnotics by men of the highest standing in psychopathology, and of newspaper items emphasizing the dangers of habit formation or referring to their employment for suicidal purposes, many physicians fear or apologize for prescribing hypnotics under any circumstances. This in my opinion is illogical, unscientific and unfair to patients, the medical profession and the public in general. The main arguments against their use, and answers to these arguments, have been given by me<sup>14</sup> elsewhere and are herewith summarized.

1 The use of hypnotics is not causal treatment, but palliative, however, symptomatic treatment is employed elsewhere in medicine.

2 There is danger of toxic effects, but their avoidance, as with other drugs, is merely a question of technic and precautions.

3 Self-medication may ensue, but with proper precautions this should not result.

4 Their use is a temporary and not permanent help or solution, but this applies to all palliative therapy.

5 It is a resort to an artificial crutch, but so are many other procedures in practice.

6 It is a line of least resistance, but it need not be so abused.

7 Other necessary treatment may be neglected by physician and/or patient, but it should not be.

8 It gives the patient the wrong idea of the causes and of the fundamental importance of the psychotherapeutic aid required, but it does not if properly handled.

9 There is danger of drug addiction.

10 The drug ordered may be used for suicidal purposes.

The last two arguments will be answered immediately. I fully endorse the views of Craig<sup>9</sup> who spoke from much experience when he said "As a profession we are unduly timid of giving hypnotics and in consequence the public, as a whole, objects to them. Brought up as I was in the same attitude, long experience has taught me the folly of such an outlook. The chief objection, I gather, is the fear of inducing a habit. Once more experience has taught me to be much more afraid of the effects of sleeplessness than of any danger of producing an addiction, a danger which is almost negligible. Let those persons who

are constantly talking about addiction produce the evidence upon which they base their statements'

Although the suicidal use of the drug ordered is apt to occur in the psychoses and alcoholism, precautions in the method of prescribing should prevent this. Suicidally inclined patients, not psychoneurotic, have many sources (newspaper items and drug stores) of information concerning hypnotics. Suicidal use is especially apt to take place in worried depressions. But an important aggravant of this possibility is the unrelieved, prolonged, marked insomnia present in such psychotic states. Psychoneurotic patients are notoriously not inclined to suicide.

Too many physicians make the mistake of misdiagnosing real mental depressions, even of the worried or agitated type, as psychoneuroses, and in such depressions the need of sufficient sleep is absolutely essential and fundamentally basic in treatment. In fact, practically all truly depressed patients with insomnia are in need of the aid of hypnotic medication since they are especially resistant to all methods of psychotherapy. Such depressed patients should, if their condition is pronounced enough, be hospitalized, hypnotics used as required, necessary precautions against suicide observed, and so-called electroshock therapy instituted when indicated. Furthermore, prolonged, severe insomnia may lead to depression and suicidal thoughts and attempts.

One of the common characteristics of depression, if not slight or mild, as in excited and other states, is the inability to secure a sufficient amount of sleep with moderate doses of hypnotics.

Craig\* was certainly fully justified when he insisted that 'As with every other disorder, the sooner we treat sleeplessness the more quickly we shall be able to correct it, and, what is most important of all, sleeplessness quickly relieved leaves no terrors behind it compared with prolonged insomnia. The physicians who are most likely to produce a drug habit are those who have permitted their patients to become terrified by the experience through which they have passed.

"In the case of hypnotics for insomnia, it is generally true that it is not the drug but the lack of confidence in the ability to sleep without it which may become a habit, with the result that they are reluctant to break away from the means which have afforded them relief."

It is our duty to see to it that patients are satisfied and relieved if at all possible by nondangerous methods adapted to the particular case. Our personal preferences should not be made rigid practices.

We surely are not justified in dismissing patients suffering from insomnia by merely telling them that it does not matter whether they

sleep or not, or that they will sleep if they will not worry about it, or to forget it.

Even if he is exaggerating his degree of insomnia, the patient must be satisfied that he is sleeping soundly and sufficiently, the general condition of the patient should always be the real guide. If the patient is in a condition in which he cannot be satisfied by explanation or by other measures, hypnotics should be temporarily used.

If you can easily and quickly produce sleep, you have a much better chance of getting a psychological hold on the patient and of increasing his confidence in himself. A period of sleep promptly given helps rapidly to break up the habit of sleeplessness, to diminish or to eliminate the other bad physical and psychological effects of insufficient sleep, and to put the patient in a psychological condition more susceptible to psychotherapy and physiotherapy. At the same time, fear of the medication given him which is so often present and deep rooted should be removed. As a matter of truth, if hypnotics are not used for insomnia, one can never be sure that other measures will produce sleep. Therefore, without the employment of hypnotics, one cannot give any definite promise of sleep on any particular night. But with medication one is fortified and can assure the patient that with a sufficient dosage and with one or the other of the hypnotics or some combination of them, sleep can positively be obtained. Furthermore, if you continue to assure a patient that he will sleep without hypnotics but his sleeplessness continues, you are gradually losing the confidence of your patient.

In fact, as Ross<sup>30</sup> says, it is certain one can be just as unscientific in withholding hypnotics as in giving them when it is not indicated.

**Technic and Precautions in Using Hypnotics**—I shall here enumerate many practical "do's and don'ts"

Deal with your patient insofar as possible on the principle of "open covenants openly arrived at"

Explain to the patient that you are using hypnotics temporarily, that you will study and treat his general condition and that hypnotics will be gradually omitted.

As many patients fear the use of hypnotics, after explaining your plan to the patient, get his views and attitude. Assure him that if he takes only what medication you order and remains under your medical supervision and sees you as frequently as you wish, he need fear neither the "dope habit" nor toxic effects.

If occasionally the patient at first prefers not to take hypnotics temporarily even when so requested by you, he will generally agree to do so after he gains more confidence in you.

All prescriptions for hypnotics or sedatives should have a "non repetatur" or "Do not refill" order

Do not prescribe hypnotic tablets or capsules by the bottle. Order only enough to last until the next visit

Do not tell the patient to take hypnotics as he needs or wishes. And do not have him renew his prescription on his own initiative or renew the prescription for hypnotics routinely by telephone. Such methods lead to self-medication with its possible dangers.

If the patient is suicidal, and this can usually be determined at the first visit, do not give the prescription or medication directly to him but to someone else (relative, nurse) who will have control of it. Such suicidal patients, of course, really need hospitalization.

Do not promise positive sleep the first night but promise that sufficient sleep can be obtained shortly with proper dosage and combination of hypnotics

Give a large enough dose at once to insure sleep, if possible, the very first night of treatment

Explain in advance some of the possible undesirable results (such as drunken feeling) the morning after taking the drug and until the dose is adjusted

After a sufficient number of good nights of sleep the usual patient readily agrees to gradual reduction of dosage until it can be omitted altogether. Sometimes at this stage if he prefers, one dose of the drug can be placed within reach of the patient to be used, if he wishes or really needs it without rising. This may give him the degree of assurance which will lead to peaceful sleep

In office practice it is best not to continue using hypnotics for more than two to three weeks or so without attempting to reduce the dose gradually

The hypnotic should preferably be varied as the patient improves or fails to get results

If permanent relief depends upon a knowledge of the cause of the insomnia and the patient refuses to cooperate in finding out the cause, one may refuse to give hypnotics until he changes his attitude.

A supply for only two or three days at a time should be ordered as a rule. In selected cases during the convalescent phase this may be somewhat extended

It is well to have at least a telephone report daily for the first few days.

See the patient, if at all possible, at least two or three times a week in the first week, the frequency thereafter varies with each case

If the patient cannot be seen frequently enough to check up on the

progress, the diagnosis, possible toxic effects, the advisability of increasing or decreasing the dose or best time of administration or of changing the medication, refuse further to treat the patient or to assume any responsibility

In the case of the average office patient I give the prescription directly to the patient or relative without fear of misuse since I have examined the patient sufficiently, have arrived at a tentative diagnosis, have made reasonably sure that he is not suicidal, have given an explanation and the plan of procedure and have had an understanding with the patient. This does not apply to depressed patients, especially if more than slightly depressed, and particularly if suspected of being suicidal, in which case, unless hospitalization seems definitely indicated, the hypnotic is under the control of someone else in the home.

If preferred, you may dispense the hypnotic yourself or have special arrangements with the druggist to give the hypnotic without the patient knowing its name.

It is much better to know a few selected hypnotics well than to know too many too little.

Use hypnotics judiciously combined with causal therapy, including psychotherapy plus any palliative physiotherapy advisable.

When, from the history and condition of the patient, real help is needed for obtaining essential sleep, hypnotics should be used not merely as a last resort and half-heartedly but promptly from the very first visit and wholeheartedly—with the practical suggestions as to technic and precautions enumerated above.

#### SO-CALLED ELECTROSHOCK AND INSULIN SHOCK THERAPY IN PSYCHOSES WITH INSOMNIA

Where insomnia is part of a psychosis, we find that, as the psychosis is improving, sleep without medication is one of the earliest signs of such improvement. This applies to the use of so-called insulin shock and electroshock treatment, which has almost universally displaced metrazol.

In depressions, including agitated depressions, in which pronounced and prolonged insomnia is common, so-called electroshock treatment produces remarkable results in a large proportion of patients, with a clearing up of the sleeplessness in many cases in a truly unbelievable manner. The patient soon gets along without drugs.

It cannot be too often emphasized that many cases of depression are wrongly diagnosed psychoneurosis and so improperly treated. Although mild depressions may be treated on an ambulatory, home-office, extramural basis, others, especially the more pronounced and

more particularly the agitated types with marked insomnia and suicidal thoughts or tendencies, need immediate hospitalization

Schizophrenic patients, especially early, may be greatly helped or may recover by so-called electroshock and/or insulin shock therapy plus psychological management

## BIBLIOGRAPHY

- 1 Kingman R. The Insomniac. New York M J & Rec., 129:683-687 130:17-21 1929
- 2 Kleitman, Nathaniel. Sleep and Wakefulness, as Alternating Phases in the Cycle of Existence. Chicago University of Chicago Press, 1939
- 3 *Ibid.*, Chapter 21. Experimental Deprivation of Sleep
- 4 *Ibid.*, Chapter 27, Insomnia or Hyposomnia, p. 381
- 5 *Ibid.*, p. 381
- 6 *Ibid.*, p. 527
- 7 Lard, Donald A. Cyclopedia of Medicine and Surgery Philadelphia F A Davis Co., 1934 Chap 11 pp 307-313
- 8 Pollock, L. J. Disorders of Sleep M CLIN NORTH AMERICA 13:1111, 1930
- 9 Muncie, Wendell. Insomnia in Clinic Psychiatric Practice Johns Hopkins Hosp Bull., 55:131-153 (Aug) 1934
- 10 Worster-Drought C. Insomnia in Early Mental Disease. The Lancet Extra Numbers No. 2 London, Wakley & Son, Chap 7, pp 37-41
- 11 Craig Maurice. The Early Treatment of Mental Disorder in Early Mental Disease. The Lancet Extra Numbers No 2, London, Wakley & Son, Chap 41, pp 191-194
- 12 Minogue, M. J. Symptoms (Insomnia) Preceding Suicide M J Australia, 2:598-600 (Oct. 31) 1936
- 13 Solomon Meyer. Shall Hypnotics Be Used in the Treatment of Insomnia in the Psychoneurosis. M. J & Rec., 138:22-26 (July 5) 1933
- 14 *Ibid.*, pp 22-25
- 15 Danziger Lewis. Specific Treatment of Psychosis Due to Estrogen Deficiency Arch. Neur & Psychiat., 51:462-468 (May) 1944
- 16 Darken, Marjorie A and Burlingame, C. Charles. Evaluation of Laboratory Controlled Estrogenic Therapy in the Psychoses. Dis. Nerv System, Vol 5, No 7 July, 1944
- 17 Danziger, Lewis, Schroeder, Harold T and Unger, Arthur A. Androgen Therapy for Involuntional Melancholia Arch. Neur & Psychiat., 51:437-461 (May) 1944
- 18 Weiss, Soma. Indications and Dangers of Sedatives and Hypnotics, with Special Reference to the Barbituric Acid Derivatives. Internat. Clinics, pp 38-66 (March) 1936.
- 19 Feiling A.. Insomnia (Use of Hypnotics) Practitioner 129:130-139 (July) 1932.
- 20 Fantus, B. Therapy of Insomnia at Cook County Hospital J.A.M.A., 102:1846-1848 (June 2) 1934
- 21 Winans, H M. Insomnia. Internat. Clin., 1:39-55 (March) 1935
- 22 Dercum, Francis X. Rest, Suggestion and other Therapeutic Measures in Nervous and Mental Diseases, 2nd ed. Philadelphia, P Blakiston's Son & Co., 1917
- 23 Diethelm, Oskar. Treatment in Psychiatry New York, The Macmillan Co., 1936.
- 24 Rosa, T A. Insomnia. Practitioner, 144:329-336 (April) 1940



- 25 Crichton-Miller, H    *Insomnia An Outline for the Practitioner* E Arnold & Co., London, 1930
- 26 Grabfield, G P    *Treatment of Insomnia* M CLIN NORTH AMERICA, 19 1597-1601 (March) 1936
- 27 Barbituric Acid and Derivatives Several contributors Pamphlet published by American Medical Association
- 28 Goodman, Louis and Gilman, Alfred    *Pharmacologic Basis of Therapeutics*, Chaps 9, 10, 11 and 12 New York, The Macmillan Co., 1941
- 29 Dejerine, J and Gauckler, E.    *The Psychoneuroses and Their Treatment by Psychotherapy* Authorized translation by Smith Ely Jelliffe Philadelphia, J B Lippincott Co, 1913, p 364
- 30 Ross, T A    *The Common Neuroses* London, Edward Arnold & Co, 1923, p 95

## INSANITY AND THE CRIMINAL

WILLIAM H HAINES, MD \* AND HARRY R HOFFMAN, MD †

MANY years ago Boswell<sup>1</sup> wrote, "Patriotism is the last refuge of the scoundrel." This could be paraphrased into, "Insanity is the last refuge of the criminal." Insanity vs responsibility has always played a rôle as a defense in criminal procedure, as many years ago courts decided that criminals found to be insane could not be held responsible for their crimes. One must remember when insanity is used as a defense it is used as an alibi. It is claimed the mind was not there, and therefore one should not be held responsible for his actions.

### HISTORICAL BACKGROUND

As early as 1625 Coke<sup>2</sup> wrote, "In criminal causes, as felony, the act and wrong of a madman shall not be imputed to him, as he is without his mind or discretion." In 1675 Sir Matthew Hale<sup>2</sup> wrote, "If a lunatic during his lunacy a man distraint by force of disease, kills himself, no felony. A man that is *non compos mentis* kills another this is no felony, the same for a lunatic during his lunacy." A lunatic was supposed to have lucid intervals during which he was *compos mentis*.

Hale also discussed partial insanity and total insanity, but admitted it was very difficult to determine the dividing line between the two. In regard to partial insanity he wrote, "This is the condition of many, especially melancholic persons, who generally discover their defects in excessive fears or griefs and yet are not wholly destitute of reason, and this partial insanity seems not to excuse them in the commission of any offense for its matter capital." And he suggests that "such a person is laboring under melancholy distempers, hath as yet, as great understanding as ordinarily a child of fourteen years hath, is such a person as can be guilty of treason or felony." In 1723<sup>3</sup> it was ruled that a man cannot be acquitted on the grounds of insanity unless he is totally deprived of understanding and memory and does not know what he is doing any "more than an infant, or a brute or a wild beast."

In 1800 James Hadfield,<sup>2</sup> a soldier, shot at King George III. At the time of the trial evidence was presented that he had been discharged from the army on the grounds of insanity, that he suffered from

---

\* Director Behavior Clinic, Criminal Court of Cook County, Illinois, 1941-

† Director, Behavior Clinic, Criminal Court of Cook County, Illinois, 1931-1941 at present, State Alienist.

attacks of maniacal frenzy and had labored under various delusions. He also said that he knew perfectly that his life was forfeited, that he was tired of life and regretted nothing but the fate of the woman who was his wife and would be his wife a few days longer, he supposed. He calmly stated that his plan was to get rid of his life by other means than suicide, that he did not intend to take the life of the King for he knew that the attempt only would answer the purpose. The Attorney-General said, in summing up his case before the jury, that according to law, "If a man be completely deranged so that he knows not what he does, if he be so lost to all sense that he cannot distinguish good from evil, and cannot judge the consequences of his action, then the mercy of the law said that he cannot be guilty of any crime because the will which, to a certain extent is the essence of every crime, is wanting. Persons of very weak understanding had committed crimes and had been punished in consequence for them though their understandings were considerably below the ordinary level because juries had decided that they had sufficient understanding to discriminate between right or wrong."

The defense attorney described Hadfield to the jury and said "He imagined that he had constant intercourse with the Almighty Author of all things, that this world was coming to a conclusion, and that, like our Blessed Savior, he was to sacrifice himself for its salvation, and so obstinately did this morbid image continue, that you will be convinced that he went into the theatre to perform, as he imagined, that blessed sacrifice, and because he would not be guilty of suicide, though called upon by the imperious will of heaven he wished that, by the appearance of the crime, his life might be taken away from him by others." The attorney referred to the words of Coke, "He that wholly loseth his memory and understanding, a prisoner, in order to be acquitted on the ground of insanity, must be a man that is totally deprived of his understanding and memory." He added, "No such madman ever existed in the world." He further said, "When a man is laboring under a delusion existing at the time of committal of the offence, and the act was done under its influence, then he cannot be considered as guilty of any crime."

The presiding judge is reported to have said, "With regard to the law, as it is laid down, there can be no doubt on earth. To be sure, if a man is in a deranged state of mind at the time, he is not criminally answerable for his acts, but the material part of the case is whether, at the very time when the acts were committed the man's mind was sane. His sanity must be made out to the satisfaction of a moral man meeting the case with a fortitude of mind, knowing he has an arduous duty to discharge." The jury found that Hadfield was in-

sane at the time he committed the act although he knew at the time of the shooting he was firing a loaded pistol at the King, and that it was an act punishable by law

In 1812 *John Bellingham*<sup>2</sup> was tried for murder for shooting a pistol in the House of Commons. He had years before been legally arrested for attempting to leave Russia while a criminal suit was instituted against him. Later he was acquitted, but he felt that the British Government should compensate him for his injuries and oppression. He had made many overtures to British officials and felt that he had not been sympathetically received. At the shooting he stood unnoticed and when someone asked "Where is the villain that fired?" he stepped up to the man and coolly said, "I am the unfortunate man. It is a private injury. I know what I have done. It was a denial of justice on the part of the government." To a friend he added, "The crime was perfectly inevitable, there was no wrong at all in doing it, he could not help that." Bellingham was sentenced to death and executed on the seventh day after the murder. The Lord Chief Justice, in summing up, said "There is a species of insanity where people take particular fancies into their heads, who were perfectly sane and sound of mind upon all other subjects, but that is not a species of insanity which can excuse any person who has committed a crime, unless it so affects his mind at a particular period when he commits the crime, as to disable him from distinguishing between good and evil, or to judge of the consequences of his actions. The question is whether you—the jury—are satisfied that he—the prisoner—had a sufficient degree of capacity to distinguish between good and evil, and to know that he was committing a crime when he committed this act, in that case you will find him guilty."

Also in 1812 *Bowler*<sup>2</sup> was tried for shooting and injuring a Burrowes with a loaded blunderbuss. Bowler was tried, found guilty and executed. At the trial he was proved to have suffered from epilepsy. He had previously threatened Burrowes and had said, "Damn that Burrowes, I will burrow him before long. I will be the death of him if I am hanged for it the next minute, so long as my name is Bowler." The judge instructed the jury "It is for you—the jury—to determine whether the prisoner when he committed the offence with which he stands charged was, or was not, incapable of distinguishing right from wrong, or whether he was under the influence of any delusion with respect to the prosecutor which rendered his mind at the moment insensible of the nature of the act he was about to commit, since, in that case, he would not be legally responsible for his conduct. On

the other hand, provided you should be of the opinion that when he committed the offence he was capable of distinguishing right from wrong and was not under the influence of such a delusion as disabled him from distinguishing that he was doing a wrong act, in that case he is answerable to the justice of his country and guilty in the eye of the law "

In 1840 *Oxford*<sup>2</sup> was tried for shooting at Queen Victoria and was acquitted on the grounds of insanity. He was a mental defective and medical testimony for the defense revealed "A deficient understanding an occasional appearance of acuteness but a total inability to reason, a singular insensibility as regards the affections. An apparent incapacity to comprehend moral obligations to distinguish right from wrong. An absolute insensibility to the heinousness of his offence and to the peril of his situation, a total indifference to the consequence of the trial, acquittal will give him no particular pleasure, and he seems unable to comprehend the alternative of his condemnation and execution, his offence is like that of other imbeciles who set fire to buildings, etc., without motive, except a vague pleasure in mischief, he appears unable to conceive anything of future responsibility." In summing up the Lord Chief Justice is reported to have told the jury, "If a man were the agent of a controlling disease which he could not at all resist, he was not then held to be a guilty party, and he would be entitled to have an acquittal upon that ground. Every case must stand to some extent on its own base. That man charged as a criminal is not responsible for the act who is, in the language of our law, 'non compos mentis'—that is, unable to distinguish between right and wrong. Every sort of insanity, and every mode of proving it, must have reference to the particular object with which it was laid before the court. Here the object was to show that at the time of committing the act the prisoner was not able to distinguish right from wrong."

In 1843 *McNaghten*<sup>2</sup> was tried for willful murder and was found by a jury to be insane. Evidence showed that McNaghten with premeditation shot his victim in the back without any altercation or any provocation on the victim's part. McNaghten, two years before the shooting, had asked his father to put a stop to a persecution that was raised against him. He thought spies were following him and had left Glasgow to avoid the spies, then went to England, and later to France. No sooner had he landed in France than the spies saw him. At the trial many prominent people testified to McNaghten's beliefs. Among the witnesses were a sheriff, a member of Parliament, a minister of the church, the provost of Glasgow and the Commissioner of Police of Glasgow.

Medical testimony by Dr E. J. Monro revealed that McNaghten said That he was persecuted by a system or crew at Glasgow, Edinburgh, Liverpool, London and Boulogne, that this crew followed him wherever he went, that he had no peace of mind, that he was sure it would kill him, that in Glasgow he observed people in the streets pointing at him and speaking of him They said, "That is the man, he is a murderer and the worst of characters." Wherever he went, in town or in country, on sea or on shore he was watched and followed

everything was done by signs he was represented to be under a delusion, and on coming out of the courthouse he had seen a man frowning at him with a bundle of straws under his arms, and the straw denoted that he should lie upon straw in an asylum In answer to questions from defending counsel, witness said "He frequently knew a person insane upon one point exhibit great clearness upon others not associated with his delusions an insane person may commit an act similar to the one with which the prisoner is charged and yet be aware of the consequences of such an act." And in cross-examination the doctor said, when asked if insanity may exist with a moral perception of right and wrong "Yes it is very common" And in re-examination he gave it as his opinion that he had not the slightest doubt the prisoner's moral perceptions were impaired, and added "I think a delusion of this nature carries a man quite away I mean that his mind was so absorbed by the contemplation of this fancied wrong that he did not distinguish between right and wrong"

Counsel for the defence, as reported by The Times, said "He did not bring this forward as a case of complete, but of partial insanity

He trusted he had satisfied the jury by the authorities he had quoted, that there existed such a disease as partial insanity or homicidal monomania, in which the unhappy patient, acting under the influence of instinct, was led on by delusion to commit crime for which morally he could not be held responsible"

The Lord Chief Justice in summing up, is reported to have said "The point which at last will be submitted to you will be whether or not on the whole of the evidence you have heard you are satisfied that at the time the act was committed, for the commission of which the prisoner stands charged, he had not that competent use of his understanding as not to know what he was doing with respect to the act itself—a wicked and wrong thing—whether he knew it was a wicked and wrong thing he had done, or that he was not sensible at the time he committed this act that it was contrary to the laws of God and man. Undoubtedly if he were not so sensible he is not a person so responsible." And later he adds "If upon balancing evidence in your minds you should think the prisoner a person capable of distinguishing right from wrong, with respect to the act with which he stands

charged, he is then a responsible agent, and liable to the penalties imposed upon those who commit the crime of which he is accused "

Following the trial of McNaghten, the House of Lords put five questions of procedure to the judges because there was a wide difference both in meaning and in words in their description of the law. From their answers is formed our legal concept of insanity of today, namely "He is punishable according to the crime committed if he knew at the time of committing such a crime that he was acting contrary to law " Because the questions<sup>2, 4</sup> are not noted in the textbooks of psychiatry, we are quoting them in full

QUESTION 1—"What is the law respecting alleged crimes committed by persons afflicted with insane delusions in respect of one or more particular subjects or persons, as for instance, whether, at the time of the commission of the alleged crime the accused knew he was acting contrary to law, but did the act complained of with a view, under the influence of insane delusion, of redressing or revenging some supposed grievance or injury, or of producing some supposed public benefit?"

*Answer 1*—"Assuming that your lordships' inquiries are confined to those persons who labour under such partial delusion only, and are not in other respects insane, we are of opinion that notwithstanding the party accused did the act complained of with a view, under the influence of insane delusion, of redressing or revenging some supposed grievance or injury, or of producing some public benefit, he is nevertheless punishable according to the nature of the crime committed if he knew at the time of committing such a crime, that he was acting contrary to law, by which expression we understand your lordships to mean the law of the land "

QUESTION 2—"What are the proper questions to be submitted to the jury when a person afflicted with insane delusion respecting one or more particular subjects or persons is charged with the commission of a crime (murder, for instance) and insanity is set up as a defence?"

QUESTION 3—"In what terms ought the question to be left to the jury as to the prisoner's state of mind at the time when the act was committed?"

*Answers 2 and 3*—"As these two questions appear to us to be more conveniently answered together, we have to submit our opinion to be that jurors ought to be told, in all cases, that every man is presumed to be sane, and to possess a sufficient degree of reason to be responsible for his crimes, until the contrary be proved to their satisfaction, and that to establish a defence on the ground of insanity it must be clearly proved that at the time of the commit-

ting of the act the accused party was labouring under such a defect of reason, from disease of the mind, as not to know the nature and quality of the act he was doing, or, if he did know it, that he did not know he was doing what was wrong. The mode of putting the latter part of the question to the jury on these occasions has generally been whether the accused, at the time of doing the act, knew the difference between right and wrong, which mode, though rarely, if ever, leading to any mistake with the jury, is not, we conceive, so accurate when put generally and in the abstract, as when put with reference to the party's knowledge of right and wrong in respect to the very act with which he is charged. If the questions were to be put as to the knowledge of the accused solely and exclusively with reference to the law of the land, it might lead to confound the jury by inducing them to believe that an actual knowledge of the law of the land was essential in order to lead to conviction, whereas the law is administered upon the principle that everyone must be taken conclusively to know it without proof that he does know it. If the accused was conscious that the act was one which he ought not to do, and if the act was at the same time contrary to the law of the land, he is punishable, and the usual course therefore has been to leave the question to the jury whether the accused had a sufficient degree of reason to know he was doing an act that was wrong, and this course we think is correct accompanied with such observations and explanations as the circumstances of each particular case may require."

QUESTION 4—"If a person under an insane delusion as to existing facts commits an offence in consequence thereof is he thereby excused?"

Answer 4—"The answer must of course depend on the nature of the delusion, but making the same assumption as we did before—namely, that he labours under such partial delusion only, and is not in other respects insane—we think he must be considered in the same situation as to responsibility as if the facts with respect to which the delusion exists were real. For example, if under the influence of his delusion he supposes another man to be in the act of attempting to take away his life, he kills that man as he supposes in self-defence he would be exempt from punishment. If his delusion was that the deceased had inflicted a serious injury to his character and fortune and he killed him in revenge for such supposed injury, he would be liable to punishment."

QUESTION 5—"Can a medical man, conversant with the disease of insanity, who never saw the prisoner previously to his trial, but who was present during the whole trial and the examination of all the witnesses, be asked his opinion as to the state of the prisoner's mind at the time of the commission of the alleged crime, or his opinion



whether the prisoner was conscious at the time of doing the act, that he was acting contrary to law, or whether he was labouring under any and what delusions?"

*Answer 5* — "We think the medical man under the circumstances supposed, cannot in strictness be asked his opinion in the terms stated, because each of those questions involves the determination of the truth of the facts deposed to, which it is for the jury to decide, and the questions are not mere questions upon a matter of science, in which case such evidence is admissible. But where the facts are admitted, or not disputed, and the question becomes substantially one of science only, it may be convenient to allow the question to be put in that general form, though the same cannot be insisted on as a matter of right."

It will be noted that the answer to Question 5 forbids the admissibility of direct questioning of the psychiatrist on the prisoner's mental condition at the time of the crime, so it is customary to put the question of insanity before the jury by means of a hypothetical question. In this question all the favorable evidence is introduced and then a hypothetical person is discussed. The jury and all in court know that it is the prisoner being discussed but he is not called by name. In many cases this is the only way that the defense can prove that a prisoner was insane at the commission of the crime. Dr William A. White<sup>16</sup> has called the hypothetical question a monstrosity.

#### BEHAVIOR CLINIC ORGANIZATION AND FUNCTIONS

In order to eliminate the so-called battle of the alienists in Chicago, in which the state and defense hired many psychiatrists, each testifying for the side by which they were retained, a committee of judges of the Criminal Court of Cook County and the Institute of Medicine in Chicago suggested the formation of a psychiatric clinic whose function would be to render an impartial psychiatric opinion to the court. From this suggestion the County Commissioners of Cook County created the Behavior Clinic of the Criminal Court in 1931. This is a branch of the Cook County Bureau of Public Welfare.

In the Behavior Clinic the examination of the criminal is made only on an order of a trial judge and consists of a physical examination, psychiatric examination, psychometric examination and a social history. A summary is prepared with conclusions and is sent to the court in triplicate so the judge may in turn give a copy to the State's Attorney and the defense attorney at his discretion.

This report to the court is limited by court order to (1) the physical findings, (2) the pertinent social history with especial attention

to any previous mental disease in the patient or his family (no mention can be made of previous penal institutions or previous criminal record), (3) the mental examination, (4) psychometric examination if pertinent. The conclusion is to state, for Criminal Court cases, whether or not active mental disease is present and the type of such disease if present, whether the individual knows the nature of his charge, and whether he can cooperate with his counsel.

In practically every case in which the Behavior Clinic is asked to make an examination, the attorneys, the patient's parents, the clergy, or some other interested person contacts the office and describes in detail the mental condition of the patient either in years past, at the time of the commission of the offense, or at the present time, suggesting that because of this erratic behavior he was not responsible for the consequence of his acts.

In addition, if the case under examination is "sensational," we receive telephone calls or letters in which the individual caller explains his theory of why the defendant committed the crime. Frequently these calls accuse the psychiatrists at the Behavior Clinic of being on the side of the state or of the defense and not giving an *unpartisan* decision. The majority of the calls are received when the Behavior Clinic reports that an individual is insane and the defendant is committed to a hospital for the criminally insane. The callers feel that justice is thwarted and do not realize that the defendant will have to stand trial upon his restoration of sanity.

Frequently the Behavior Clinic is asked by the court to examine a prisoner who refuses to cooperate for an examination. This refusal on the part of a defendant to permit examination is usually on the advice of his counsel, especially if the defense intends to employ its own psychiatrists. The law does not force a defendant to submit to an examination, so that his refusal to cooperate with the court psychiatrist constitutes the highest degree of cooperation with his own counsel. When refusal to cooperate is reported to the court, it can be inferred that the defendant is sane. Occasionally a defendant may not cooperate with the state's attorney when his statement is taken and may give the state's attorney irrelevant answers to suggest insanity or simply indifference. However, he tries to cooperate with the court psychiatrist. One exmillionaire of the prohibition era responded flippantly and irrelevantly to each question the state's attorney asked him prior to his trial. At the psychiatric examination he told of his vast estates with golf courses private chauffeur for each of his children, and his ability to "buy" state's attorneys at 'a dime a dozen in the old days.' However, he added, "There is just one man I'm afraid of and it's the

'bug' doctor If you find me insane, I'll be sent to an institution for the criminally insane and it will be months before I can put the machinery in order to get out" With his own lawyer and the psychiatrist he cooperated fully

#### LEGAL CONCEPTIONS OF INSANITY

If at any time the question of insanity is raised by either the defense or prosecution and it is called to the attention of the court, it is mandatory that a jury be impaneled and a civil trial be held to determine the defendant's mental condition Under our law, a man is always considered sane until proved insane If a defense attorney permits his client to enter a plea on arraignment for the charge, it is the same as admitting that he is competent and therefore sane He, however, can always use insanity at the time of commission of the act as a defense To do this, he must present testimony to that effect during the trial and then by means of a hypothetical question have the alienist give his opinion of the mental state of a hypothetical person at the time of commission of the crime

One must bear in mind that the legal conception of sanity differs at times from the medical interpretation of mental disease Insanity is a legal term applied to the individual's responsibility for his behavior His lack of responsibility may be due to mental disease or mental defectiveness This condition of insanity may be inherent in the individual or it may be acquired With this in mind, we can easily postulate a number of variations in the state of an individual's sanity before and during a criminal trial, namely He may be (1) insane at the commission of the crime and have recovered from his insanity at the time of the trial, (2) insane at the commission of the crime and still insane at the time of the trial, (3) sane at the commission of the crime and insane at the beginning of the trial, (4) insane during the progress of the trial, (5) sane during the trial and insane before pronouncement of sentence, (6) sane at the pronouncement of sentence and insane before execution of the sentence

The Supreme Court in Illinois in separate decisions have defined the tests necessary to declare a defendant insane at the different stages of his trial These are

*At Commission of a Crime* <sup>6</sup> "When an accused is put on trial for a crime or misdemeanor, the correct test as to insanity is whether or not the defendant is capable of knowing right from wrong as to the particular act in question and is capable of exercising the power of choosing either to do or not to do the act and of governing his conduct in accordance with such choice"

*Before Trial* <sup>7</sup> "He is not considered a lunatic or insane if he is capable of understanding the nature and object of the proceedings against him, and if he rightly comprehends his own condition in reference to such proceedings and has sufficient mind to conduct his defense in a rational or reasonable manner, although upon some other subjects his mind may be deranged or unsound "

*Before Judgment* <sup>8</sup> "A person that becomes lunatic or insane after the commission of a crime or misdemeanor shall not be tried for the offense during the continuance of the lunacy or insanity If, after the verdict of guilty, and before judgment is pronounced, such person becomes lunatic or insane, then no judgment shall be given while such lunacy or insanity shall continue And if, after judgment and before execution of the sentence, such person becomes lunatic or insane, then in case the judgment be capital, the execution thereof shall be stayed until the recovery of said person from the insanity or lunacy In all of these cases, it shall be the duty of the court to impanel a jury to try the question whether the accused be, at the time of impaneling insane or lunatic."

*Before Execution* <sup>9</sup> "The defendant before execution is to be regarded as sane and not lunatic, when he has sufficient intelligence to understand the nature of the proceedings against him, what he was tried for originally, the purpose of his punishment, the impending fate which awaits him, and a sufficient mind to know any facts which might exist which would make his punishment unjust or unlawful and sufficient of intelligence to convey such information to his attorney or the court. When he has not such intelligence and mental ability he is to be regarded as insane or lunatic by the verdict of the jury, if so found, and his execution stayed or prolonged "

#### MALINGERING

In examining criminals for their mental condition when up for trial, the question of malingering must always be borne in mind In civil practice the patient's statements regarding delusions and hallucinations are accepted, and if in the opinion of the doctor the patient is committable, he is certified and committed to a proper hospital In the case of the criminal, especially if he is facing the electric chair or a long sentence, one must be very suspicious of any psychotic manifestations. His background, former associations and previous history must be scrutinized carefully, he must be observed, unbeknownst to him, for peculiar behavior The guards, especially on the night shift, should be interviewed regarding his cooperation and behavior on the tier

One patient examined by the Behavior Clinic, charged with murder, used insanity as his defense. When he came into the court room he presented a disheveled appearance, made many facial grimaces, at times had to be held down and was handcuffed. He attempted to disrobe before the women jurors and frequently opened the front of his trousers. Once during the trial he removed his shoes and stockings and kicked them away from where he was sitting. The trial was in the winter time and the stone floor of the court room was cold. It was observed that in his antics he tried gradually to draw his socks close to his chair so that he could rest his feet on them rather than on the cold floor. Later that night when he entered his cell, although in the court room he appeared to be totally bereft of reason, he asked the guard if he could stay up until the early morning edition of the newspaper arrived so that he could read the account of his trial. Later it was learned that the defendant's sister took lessons in stage technique so that she could make a favorable and dramatic impression before the jury as a witness for her brother.

In another case in the mental examination we elicited many delusions and hallucinations. The family came from a nearby town and gave essentially the same story as the prisoner. However, it was found that the defendant had formerly been an attendant in a state hospital, and when it was explained to him that he would be sentenced to a hospital for the criminal insane, and not the hospital where he was formerly employed, he immediately changed his story and confessed that his plan was to go to the state hospital and then run away through the help of friends.

In malingering the criminal usually changes his behavior immediately upon seeing the examining doctors. When he knows the doctor will not be around, he plays cards and carries on the regular jail routine. It is difficult for a malingerer to carry out the same behavior pattern daily for weeks, although it has been done. It is sometimes months from the time a man is arraigned before he is brought to trial so that during the interval he can be watched constantly.

Another criminal who was up for a murder made a suicidal attempt at the jail and was placed under careful, constant supervision. When seen by the doctors, he was apathetic, stared into space, and appeared to be responding to auditory hallucinations. His wife gave a detailed history of psychotic behavior for three years, following a head injury. However, upon questioning the guards, it was found that in the evening the prisoner worked crossword puzzles and played checkers with the other inmates. Three days prior to his trial he refused to eat and had to be carried to the court room. Just prior to this a letter was intercepted in which he outlined each step that

should be taken to prove his insanity, saying in part, "I am not supposed to be aware of anything, as I am supposed to be crazy. I want to impart some information to you which you in turn will give to the lawyer representing me. Don't you realize that my life hangs in the balance, that everything depends on you, as I put my trust in you? So please, for God's sake, heed my words. Don't you realize that they want to make an example of me and put me in the electric chair even though they may not be able to do it if I go to trial. It is too late to turn back now. I have gone too far and they are mad at me because if I am pronounced insane it will spoil the State's case and they will have to commit me to the Psychiatric Division until I am cured, and then I will come back and have a chance to beat the rap, because I can contend that I was not responsible for my actions. After you have copied the information burn this letter up. I want you to volunteer this information of your own accord because you naturally know all about my life." He then gave a list of friends to call upon to testify that he gave the impression of being 'unstable, irrational and unsettled', that he would always lose interest in things he was doing, he would begin a conversation and suddenly stop in the middle of it and start roaming, that he would sit and stare into space for long periods of time, and would pay no attention to those about him. He advised that all his friends be informed of this and then that they be subpoenaed to testify in court. In a twelve-page letter he outlined the steps one by one. Confronted with this evidence, his behavior changed immediately. He submitted to the mental examination and no overt signs of mental disease were elicited.

Frequently it is difficult to convince a jury that a criminal is malingering, especially if he presents many bizarre mannerisms, answers questions irrelevantly and shows peculiar behavior.

Evidence was presented to the court at the trial of one prisoner who was charged with murder that the behavior of the prisoner changed the moment a psychiatrist entered the cell tier, that if playing cards he would fall on the floor and remain there until the psychiatrist left. On one occasion he was smoking a cigarette and, upon seeing the doctor, assumed a catatonic posture, letting the cigarette burn his fingers and dropping the same when the burn became painful. At his sanity hearing he had to be carried to the witness stand, made many awkward and purposeless movements and responded irrelevantly to questions but when told to leave the stand he immediately walked to his seat. Although the psychiatrist testified that he was malingering, the jury found him insane and he was committed to a hospital for the criminal insane. After a month in the hospital for the criminal insane, he stated he would rather be tried for his offense than to spend his time with the "nuts."

On another occasion two psychiatrists testified that a criminal was insane and just before the jury was to leave the room the defendant demanded that he be heard. He testified that he stole the car by remote control, that he tried to flood the jail so that he could swim out between the bars, and then stated that he wanted to return to his mother. With this statement he broke into profuse tears and cried loudly. The jury then went to the jury room and returned with a verdict of sane. The judge sentenced him, asking him if he wished to make a statement, to which he replied "Let's match, Judge, for one to ten or one to twenty." Upon arriving in the state penitentiary he was promptly transferred to the Psychiatric Division of the prison.

#### MENTAL RETARDATION

Mental retardation constitutes a frequent defense by the relatives and attorneys of criminals. If the criminal has ever been in an institution for the feeble-minded, in an ungraded room in school, or did not finish the prescribed school course, this is brought to the attention of the Behavior Clinic. Before one can be tried on a criminal charge, he must have his rights restored from any previous commitment either as feeble-minded or insane. In the lower courts, it is customary to commit individuals to institutions for the feeble-minded when the I Q is 70 or below. These individuals often escape or are brought home on a parole and get into subsequent difficulties.

The Supreme Court of Illinois reviewed the case<sup>10</sup> of a boy who was adjudged feeble-minded and committed to a state hospital for the feeble-minded at the age of 17 by the Juvenile Court of Cook County. In the order of commitment it was recited, "and the court hereby retains jurisdiction of this case for the purpose of making such further or other orders herein for the welfare of said person as may from time to time be found to be in accordance with equity and in accordance with the statute in such case made and provided." Later the boy escaped from the state hospital for the feeble-minded, and in the course of a hold-up killed a man. He signed a confession and when arraigned entered a plea of not guilty. He was examined by two psychiatrists and after their reports were given to the court the plea was changed to guilty. The defense attorney informed the court that his client understood the proceedings and the court, after warning, permitted him to plead guilty to the charge of murder. He received the sentence of death. Some time later a petition to vacate the judgment and sentence was filed. The petitioner alleged that because of his ignorance of the facts he improperly advised the boy to enter a plea of guilty and that, acting upon the petitioner's advice, the boy entered such a plea under a misapprehension. This petition was denied.

Thereafter a second petition to vacate the judgment and sentence was filed by an attorney not connected with the case previously. This petition stated that after the boy had been indicted in Criminal Court for robbery, the Juvenile Court, upon a transfer of the cause from the Criminal Court, took jurisdiction of his person.

In support of this petition an affidavit was filed by the attorney who represented the boy upon the entry of the plea of guilty. The attorney, after setting forth the commitment of the plaintiff in error to the state hospital and his escape therefrom, averred that he was not aware a plea of guilty could admit the capacity of the boy to commit the crime therein charged, that he was not familiar with the law in regard to feeble-minded persons, that he did not know the legal effect of the adjudication of the Juvenile Court, and that because of his ignorance and inexperience he advised the entry of a plea of guilty when he should have pleaded the want of jurisdiction of the Criminal Court. This petition was also denied.

The Supreme Court contended that the trial court erred in not vacating the judgment and sentence upon disclosure that the Juvenile Court had adjudged the boy a feeble-minded person and retained jurisdiction over him and that the decree was in force when his plea of guilty in the present case was entered. The criminal code required that before a plea of guilty may be entered, the court shall fully explain to the person accused the consequences of entering such a plea. A plea of guilty should be entered only when a person making it is of competent understanding and has been fully informed respecting the consequences of the plea. The plea would be of no effect if the explanation required by the foregoing section were not first made, and an explanation or warning could be of no force unless the person accused were mentally competent to understand it.

A plea of not guilty would not necessarily admit the mental competency of the person entering it, and would be consistent with a contrary contention, while a plea of guilty is inconsistent with mental incompetency, especially as it is defined in the statute under which the boy was adjudged feeble-minded. The statutory definition is: "Any person afflicted with mental defectiveness from birth or from an early age, so pronounced that he is incapable of managing himself or his affairs, or of being taught to do so, and requires supervision, control and care for his own welfare or for the welfare of others, or the welfare of the community." This definition, though slightly different from the statutory definition of insanity, is predicated upon mental incompetency. The general rules of law applicable to an insane person in respect to his mental competency would apply to a



feble-minded person where the defect amounts to the same lack of capacity. As a general rule, where insanity or mental incompetency is proved as existing at a particular period, it will be presumed to continue until disproved. Thus, a decree entered finding a person feble-minded shall stand and continue binding upon all persons whom it may concern until rescinded or otherwise regularly superseded or set aside. In this case of the death sentence the judgment was reversed and the cause remanded. At the subsequent trial the boy received a 100-year sentence.

Thus it will be seen that the sanity tests for feble-mindedness in the State of Illinois are the same as for insanity, and there has to be a marked degree of mental enfeeblement if a defendant cannot cooperate with his counsel or know the nature of the charge against him. On one occasion the psychiatrist testified that a man with an I Q of 44 could not cooperate with his counsel but that he knew the nature of the charge. The judge berated the psychiatrist before the assembled court, stating that in all previous testimonies he had agreed with the psychiatrist, but in this case he did not agree. The judge felt that even if the I Q were 44 the patient could cooperate with his counsel in the proper presentation of his case. The patient presented a good personal appearance and tried to answer questions. He made a plea to the court that he be released, as he wanted to marry the daughter of his godmother. When the godmother was asked about this she stated that her daughter was just a small child when the defendant was committed, that in the interim no one had communicated for him with her or any member of her family, and that she was certain her daughter was unaware of his intentions. He was charged with taking from the mails an eighteen dollar check three years before. He had been in an institution for the criminal insane in the meanwhile. He was able to tell the judge's name, the charge under which he was held, where he had worked, and the names of a few streets in Chicago. The judge offered this as evidence of cooperation. Then the attorney for the state asked the defendant if he had twenty dollars and spent eighteen dollars how much money he would have left, after a considerable period of time he replied he did not know. Evidence was presented in court that the defendant had reached the eighth grade in school but had been passed each year, finally leaving school at the age of 16. No records had been kept on his grades and no reason was given for his yearly promotions. He was unable to read or write. His mother was psychotic and she was the only living relative. With this evidence the judge sustained the testimony of the psychiatrist that the defendant was feble-minded.

In our experience many individuals who have been committed to institutions as feeble-minded are later found to have average, if not superior, I Q's.<sup>1</sup> It must be remembered, in evaluating I Q's, that they are never lower than estimated but may be higher, depending upon the cooperation of the person and the seriousness of the offense. One criminal with a long record who was at one time committed as feeble-minded had an I Q of 75. His psychiatrist testified that the criminal could not spell his name and that he himself considered all with an I Q of below 80 as feeble-minded and committable. At the trial it was brought out that the defendant signed his confession and jail entrance card correctly. This convinced the jury that he was of average intelligence and they returned a verdict accordingly.

We have found from experience that unless a defendant is actively hallucinating or has a history of previous hospitalization or attempts at suicide, or acts up in court, the jury will, in most instances, find him sane even if all the testimony is to the contrary. Likewise in cases of feeble-mindedness if the defendant presents a neat appearance is able to tell his name, the date, and answer correctly questions of simple calculation he will be found not feeble-minded. Occasionally the jury presents a verdict which is contrary to the evidence introduced. For instance if the only witness, a psychiatrist, testifies that the defendant is insane in some instances a verdict of "sane" is returned and the reason for the verdict, as explained by the jury, is their feeling that the defendant is trying to escape trial and punishment.

#### FUNCTION OF PSYCHIATRIST

To help determine the defendant's responsibility is the object of the psychiatrist in court. It is the function of the jury<sup>21</sup> to decide if the defendant is sane or insane and the psychiatrist must not usurp the function of the jury. He may express his opinion and give the facts on which he bases his opinion. As the jury determines the defendant's sanity is of a civil nature not criminal, either side may call the defendant as a witness. In uncontested cases the defendant is seldom put on the witness stand and examined so that the psychiatrist is usually the only witness. The sanity jury cannot decide the guilt or innocence of the defendant nor can it make recommendations.

The psychiatrist<sup>12</sup> must always make a copy of the questions asked and the answers returned in the examination of a defendant. It is important to record the amount of time spent in the examination and the number of examinations made. The jury will be more favorably impressed by one who has examined a defendant on several occasions than one who has seen the defendant only once. In examinations by

order of the court all conversation can be presented before the jury. Care must be taken not to ask leading questions regarding mental illness or symptoms. Recently a young man was tried for murdering his sweetheart in a theater. A psychiatrist testified in court that the defendant was hearing the voice of his dead father talking to him at night in his cell. After this testimony was introduced in court, a guard asked the defendant the following day, "When did you ever hear voices?" To which he replied, "I didn't until they told me about it."

### ALCOHOLISM

The majority of crimes of all types are committed under the influence of alcohol, or there is a history of imbibing some time prior to the crime. Records of the Behavior Clinic show 41 per cent of defendants with a history of drinking or intoxication at the time of the crime. In addition to this 11 per cent give a history of mild drinking on other occasions, 5 per cent report a history of alcoholism in either or both parents although the defendant himself does not drink, 45 per cent report abstinence from alcohol except on social occasions. It must be remembered that when in the state of voluntary intoxication one is subject to the same rules of conduct and the same principles of law as a sober man. Occasionally following alcoholism there is amnesia for the period of the offense and some time afterwards, possibly hours to days. The individual is able to recount his behavior up to the time he started to imbibe. His next recollection is usually the awakening in the police cell. On occasion an acute psychotic reaction may follow through fear, anxiety, suspense or stories told him by his fellow inmates.

### EPILEPSY

Any mental deviation, no matter how slight, is considered by the defense as an excuse for commitment to a state hospital in order to dispose of the case and escape sentence. It is difficult to convince relatives and defense lawyers that psychoneurotics and psychopaths are responsible for their actions and behavior. One factor stands out, and that is that epilepsy has not been used as a defense, perhaps due to the ignorance of the defense attorney on this subject. Epilepsy is prevalent in hospital out-patient clinics, but in jail it is seldom seen and when present in a defendant it has not been used as a mitigating circumstance in the experience of the Behavior Clinic. We would expect to see furor states used as an explanation of some of the serious and offensive crimes.

## THE JUDGE'S INSTRUCTIONS TO THE JURY

Prior to the deliberation of the jury on the sanity issue the judge instructs as follows 'On this hearing the jury is instructed not to consider the question as to whether the defendant in this case is guilty or not of the crime charged. The only question to be determined by you is whether or not this defendant has sufficient mentality to be tried

"After considering all the evidence in this case, if you are convinced by a preponderance of the evidence that this defendant is insane to such an extent that he does not understand the nature of the charge against him and, further, that he is unable to fully cooperate with his lawyer in a proper defense of the case, you will find by your verdict that the defendant was at the time of the impaneling of this jury, and now is, insane

'On the other hand, if you find from a preponderance of the evidence that the defendant in this case fully understands the nature of the charge and is fully able to cooperate with his counsel in a proper defense of his case, you will, by your verdict, find that the defendant at the time of the impaneling of this jury was, and now is sane

In feeble-minded cases the word "insane" is replaced by "feeble-minded"

If there is a history that the defendant has been in a state institution in any state, the following form of instruction is used. The court instructs the jury as a matter of law, that in this proceeding the jurors are not determining the guilt or innocence of the defendant. The jury is called upon only to determine from the evidence in this case whether the said at the time of the impaneling of this jury has permanently recovered from his insanity. In determining that question, the jury will be governed by this test only, did the said at the time of the impaneling of the jury, and now, have sufficient intelligence to fully understand the nature of the charge against him and have sufficient intelligence to understand the proceedings and sufficient mind to know any facts which might exist which could be used in his defense, and sufficient intelligence to convey such information to his attorney or to the court? If he did, then he is regarded as having permanently recovered from his insanity'

## CONCLUSION

1 Any individual adjudicated insane or feeble-minded must have a restoration from his previous commitment before the state can institute criminal proceedings. The test for feeble-mindedness is the same as for insanity in Illinois.

2 By recent enactment in the State of Illinois<sup>13</sup> the term "insanity" is to be applied only to criminal cases The term "mental illness" is to be used in reference to civil cases

3 We wish to suggest that society would be better protected if all persons were tried on the charges for which they are indicted, and a verdict entered Then, if the defendant is found not guilty and was insane, he could be committed to a state hospital for mental illness, or, if found guilty and the charge is a minor one, the charge could be dropped and he could be committed to a state institution where he could receive medical attention If guilty and the maximum security is desirable, he could be committed to a state hospital for the criminal insane, there to await his recovery At the present time many are found insane at the time of going to trial, and in a few years, when all witnesses and evidence have disappeared, they are restored as recovered It is necessary to dismiss the charges against them for lack of prosecution, and the individual goes free

#### BIBLIOGRAPHY

- 1 Boswell, Samuel *Life of Dr Johnson*, Vol I, p 7
- 2 East *An Introduction to Forensic Psychiatry*, Chap III Baltimore, Wm Wood & Co, 1927
- 3 Rex, Arnold A.D 1723, as quoted in reference 2
- 4 Mercier *Criminal Responsibility* New York, Physicians & Surgeons Book Co, 1926
- 5 *100 Years of Psychiatry*, Chapter on Legal Aspects of Psychiatry New York, Columbia University Press, 1944
- 6 *People v Lowhone*, 292 Illinois 32
- 7 *Freeman v People*, 4 Denis, 9
- 8 *People v Geary*, 298 Illinois 241 (Hurd's Stat 1917, p 1016)
- 9 *People v Geary*, 298 Illinois 245
- 10 *People v Varecha*, Docket 21849-April 1933 (Illinois)
- 11 *People v Geary*, 298 Illinois 246
- 12 Williams *The Insanity Plea* Baltimore, Williams & Wilkins Co., 1931
- 13 *Illinois Mental Health Act*, 1943

## CLINICS ON OTHER SUBJECTS

### USES AND ABUSES OF QUINIDINE

J BAILEY CARTER M.D.\*

QUINIDINE was first described, in 1848, by van Heyningen. It was first prepared and named by Pasteur in 1853. Quinine was used for many years for its sedative action on the heart. In 1866 Oppolzer said, "The best and most powerful factors in dealing with heart patients are three—rest, digitalis and quinine." Because of the lack of proper indications for its use and its paralyzing effect on the heart, clinicians abandoned the use of quinine. Wenckebach's attention was directed to it in 1912 by a Dutch merchant who used it to control his paroxysmal auricular fibrillation. In 1914 Wenckebach recorded the first deliberate use of it in the treatment of this condition. He exploited the very quality which had caused older clinicians to abandon the drug. In 1910 Frey studied the clinical pharmacology of the various cinchona alkaloids and found quinidine more effective than quinine, the difference being merely quantitative, the ratio 2:1.

#### PHARMACOLOGIC EFFECTS

Quinidine is the dextro-isomer of quinine. Both are protoplasmic poisons but quinidine is less toxic. Both depress the heart muscle. Quinidine impairs refractoriness more than contractility and is the drug of choice in cardiac arrhythmias.

#### PERTINENT PHYSIOLOGY OF THE HEART

The *normal heart beat* arises in the sinus node and spreads in orderly fashion and definite sequence to activate auricles and ventricles. A heart beat that originates elsewhere, in auricles or ventricles is *ectopic* (abnormal) in origin. A series of two or more such beats constitute an *ectopic rhythm*. The abnormal rhythm may be *passive*, the result of depression of the sinus node or blocking of the impulse, or it may be *active*, the result of increased irritability of an ectopic focus. With such a focus irregularly active, *extrasystoles* of auricular A-V nodal or ventricular origin, occur. A run of two or more such

---

From the Department of Medicine, Cook County Hospital, Chicago.

\* Assistant Professor of Medicine (Rush) University of Illinois College of Medicine.

beats constitutes *paroxysmal tachycardia* which may be auricular, A-V nodal or ventricular in type. A very rapid coordinate ectopic rhythm constitutes *auricular flutter*. Similar but incoordinate activity is characteristic of *auricular fibrillation*. Rapid incoordinate heart action may involve the ventricles as a terminal or, rarely, transitory event known as *ventricular fibrillation*. *Chaotic heart action* results if multiple ectopic foci are simultaneously active, the extent of this *combination of arrhythmias* depending on their number and location.

#### BEDSIDE DIAGNOSIS OF ABNORMAL RHYTHM

Exercise, amyl nitrite and atropine increase the rate of normal (sinus) rhythm. A persistent irregularity above 120 is more likely, if above 140 practically always, *auricular fibrillation*. The ventricular rate rarely exceeds 180 per minute. Exercise increases the irregularity. Innocuous arrhythmias disappear with increase in heart rate.

In *auricular flutter* the rhythm is usually regular. The relation of auricular rate (280 to 360) to ventricular rate (140 to 180) is due to 2:1 A-V block. With arrhythmia from irregular block, exercise often makes the rhythm regular. Exercise does not usually affect the rate. Vagal stimulation often causes temporary slowing, usually at half the rate, which promptly returns to the original rate when stimulation ceases. It may be ineffective, or irregular heart action may accompany the slowing.

In *paroxysmal tachycardia* the rate varies from 150 to 250 per minute. Sudden onset and cessation of a paroxysm is characteristic. In the common, benign, auricular form the rhythm is regular. In the rare but serious ventricular type the rhythm is slightly irregular, the counts varying 4 to 8 beats per minute. Exercise does not affect the rate. Vagal stimulation abruptly stops the mechanism (50 per cent) or has no effect (50 per cent).

*Extrasystoles* of A-V nodal or ventricular origin have a compensatory pause. The pause after auricular extrasystoles is short. Extrasystoles are more frequent in the supine than in the upright position. The arrhythmia usually disappears with increase in heart rate.

#### CIRCUS MOVEMENT

The conception of a "circus movement" of the excitation wave as the cause of flutter and fibrillation dates from Mayer's observations on Medusa in 1908. He induced a circus movement in the umbrella of the jellyfish by creating a local block and applying a stimulus to one side of the blocked region. The resulting contraction wave, due to the block, was forced to take an "unidirectional" course. If, after

completing the circuit the tissue from which the wave had been initiated was no longer refractory but excitable, it circled the ring again and again. If the disk was stimulated in the absence of block, the waves spread in both directions, completed half of the circumference of the disk, met and were suppressed since each was arrested by the refractory region of tissue occupied by the other. *Local blocks* rather than increased excitability is the essential factor in circus movement. A wave deflected into a circular course by local blocks can continue to circulate only if a gap of responsive tissue exists between the crest and the tail of the wave. The shorter the refractory period, the slower the transmission or the longer the path, the wider will be the gap. Closure of the gap by altering one of these conditions brings the circus movement to an end.

In the mammalian auricle, immediately after the passage of an impulse, some fibers recover more promptly and are able to respond to the next impulse while others are still refractory. This period of *partial refractoriness* creates *multiple blocks* in the auricular muscle. Since the excitation wave can spread only over responsive fibers, it is deflected from its normal course and forced to weave its way through the auricular muscle by a more devious course, its *transmission time* being considerably delayed. Conductivity is not impaired but the longer path of the impulse has the same effect. Prolonged transmission time combined with shortened refractory period permits the impulse to continue to circulate. Prolonged refractory period or shortened transmission time (due to quicker conduction or shorter path) tends to close the gap between the head and tail of the wave and to bring the "circus movement" to an end.

#### AURICULAR FIBRILLATION

This is the most common persistent arrhythmia. Except in hyperthyroidism it is rarely seen in the absence of definite organic heart disease. It is common in mitral stenosis, thyrotoxicosis, arteriosclerosis and hypertension. It is rare in aortic disease and in subacute bacterial endocarditis. In the *paroxysmal* type, the patient may suddenly develop tachycardia, palpitation, precordial pain, dyspnea, vertigo, nausea, pallor or even collapse. These attacks are often associated with hyperthyroidism, undue exertion, acute infection or the use of drugs, alcohol or tobacco. Recurrent or persistent attacks give rise to the *chronic* form, common in heart failure, a result of the persistently increased intra-auricular pressure. No characteristic pathologic lesion can be identified as responsible for the onset or continuance of auricular fibrillation.



The orderly sequence of auricular contraction is replaced by a self-perpetuating excitation wave within the auricular muscle. The engorged and functionless auricles show rapid, futile, fibrillary twitchings at a rate of 450 or more per minute. The ventricles, unable to respond to but relatively few of these auricular stimuli (because of functional A-V block), usually have a rate of about 120 and rarely over 140 per minute. Their contractions are totally irregular both as to force and rhythm. This rapid, irregular heart action leads to inadequate diastolic ventricular filling with resultant inability of weak contractions to open the aortic valve leaflets. A *pulse deficit* results, the difference in heart rate at apex and radial pulse varying from 10 to 100 beats per minute.

Fibrillation and flutter are similar in nature. Fibrillation is due to a circus movement within the auricular musculature which travels at a variable rate and follows an inconstant path. Flutter is due to a circus movement within the auricular muscle which follows a constant path at a constant rate.

**Effects of Quinidine on the Heart**—Therapeutic doses (1) *prolong the refractory period*, often by 50 to 100 per cent, (2) *slow the transmission* of the cardiac impulse, in heart muscle and from auricles to ventricles, (3) *increase the amplitude of contraction*, the prolonged refractory period with its resultant slower rate permitting increased diastolic ventricular filling, (4) *decrease myocardial excitability* by increasing the refractoriness of auricles and ventricles, (5) *slow the heart rate* by increasing the refractoriness of the sino-atrial node, which decreases the rate of impulse formation.

**Effects in Fibrillation**—Quinidine prolongs the refractory period of auricular muscle. Circus movement tends to die out due to inexcitable tissue in its path, i.e., "The head of the circulating wave catches up with its tail." The auricles become quiescent. Dominance of the sino-atrial node then initiates regular rhythm.

**Quinidine and Digitalis**—Quinidine cures auricular fibrillation by restoring regular rhythm. Digitalis does not cure it but, by its effect on auriculoventricular conduction, causes the ventricles to beat more slowly, regularly and efficiently. Both drugs prolong the refractory period and slow conduction. Their mechanisms of action differ radically. Digitalis increases the force of myocardial contraction. Quinidine depresses the restorative metabolism of the myocardium. The predominant action of quinidine is on the auricles, that of digitalis, on the ventricles. Digitalis counteracts the depressant (toxic) action of quinidine on the myocardium. Quinidine counteracts the toxic ac-

rhythmias of digitalis With toxic doses, digitalis causes systolic, quinidine diastolic arrest of the heart

**Toxic Reactions from Quinidine**—Undesirable effects may be the result of the drug or of the diseased heart plus the drug

*Idiosyncrasy* explains the sudden appearance of cinchonism which may follow a small therapeutic dose This is uncommon

*Cinchonism* is due to overdosage or idiosyncrasy. Tinnitus, vertigo, blurred vision, photophobia, diplopia, scotomata and dilated pupils may develop Amblyopia is usually associated with retinal ischemia Amaurosis may be followed by optic atrophy Respiratory distress, asthma or temporary cessation of breathing may occur, as may nausea, vomiting, abdominal pain and diarrhea Headache, fever, apprehension, excitement, confusion, syncope, delirium and coma have been noted Renal damage, with anuria and anemia, has been ascribed to quinidine The skin is often flushed and sweating Rashes, angio-neurotic edema or inflammatory swelling may appear

*Tachycardia* due to flutter during the transition of fibrillation to regular rhythm may be dangerous

*Ventricular fibrillation* is responsible for many fatalities previously attributed to embolism Antecedent tachycardia can often be prevented by previous digitalization

*Ventricular standstill*, temporary or fatal, may occur during the period of auricular quiescence, due to sino-atrial and/or auriculoventricular block

*Embolism* has been overemphasized It is no more frequent with proper quinidine therapy than with digitalis or no medication

#### Contraindications to Quinidine Therapy.—

- 1 Idiosyncrasy
- 2 Severe cinchonism
- 3 Acute infection
- 4 Bacterial endocarditis
- 5 Extensive myocardial disease as evidenced by
  - (a) Cardiac hypertrophy or enlargement
  - (b) Valvular disease and/or
  - (c) Fibrillation of long standing
  - (d) Coronary occlusion
  - (e) Heart failure
- 6 Aged patient or one in whom a return to regular rhythm is unlikely or is not particularly desirable
- 7 Hyperthyroidism prior to thyroidectomy Normal rhythm often reappears after operation. When fibrillation is stopped by quinidine before operation it may reappear afterwards

- 8 Angina pectoris, relieved by the onset of fibrillation
- 9 Embolism usually precludes use of the drug with safety, although recurrent episodes in an otherwise benign fibrillation may justify its use
- 10 Complete heart block Nothing is gained by restoring regular rhythm The ventricular rate is increased, extrasystoles appear, tend to form groups, and may initiate an attack of ventricular tachycardia or fibrillation Partial block is not a contraindication but indicates careful graphic control of therapy Progress of a conduction defect or the onset of a new, abnormal rhythm prohibits further use of the drug

Contraindications cannot be absolute Each case is a law unto itself

#### Indications —

- 1 Auricular fibrillation persisting more than three days after thyroidectomy \* Regular rhythm is restored in 90 to 95 per cent of these cases Delay increases the percentage of failures
- 2 Young patient with little heart damage but with a distressing arrhythmia of recent origin
- 3 Arrhythmia after, not during, an acute infection or following operation
- 4 Patient whose chief complaint is intractable palpitation in spite of all other treatment
- 5 In otherwise hopeless cases when all other therapy has failed
- 6 In mitral disease with persistent extrasystoles and in fleeting, distressing, undiagnosed arrhythmias quinidine may delay the onset of auricular fibrillation

**Absorption and Excretion**—Quinidine is readily absorbed and quickly excreted in the urine Cumulative effects need not be feared Relatively large dosage at short intervals is essential to successful therapy

**Preparations**—Quinidine sulfate, the official USP preparation commonly employed, occurs as fine, needle-like, white, odorless, bitter crystals which darken on exposure to light It is soluble in water (1 90) and in alcohol (1 10)

**Clinical Uses**—Quinidine decreases morbidity but does not reduce mortality The presence of auricular fibrillation, per se, is not an indication for its use An adequately digitalized, chronically fibrillating heart is no less efficient than it is after restoration of regular rhythm by quinidine If such a patient is heart conscious or uncom-

\* The incidence of auricular fibrillation in thyrotoxicosis is from 5 to 10 per cent. After operation 45 per cent of cases return to regular rhythm and 15 per cent more revert eventually In 40 per cent of cases fibrillation continues after operation, unless quinidine is used

comfortable or if his activity is restricted because of palpitation, quinidine may be helpful. Some patients are more uncomfortable after restoration of regular rhythm than with fibrillation. Digitalis is indicated in heart failure and subsequent use of quinidine is seldom justifiable or successful. The advisability of combined therapy is questionable. Digitalis should be used in most cases of fibrillation. Quinidine is indicated in relatively few instances. Digitalis to slow tachycardia before using quinidine is advisable. Persistent postoperative fibrillation in thyrotoxicosis and arrhythmias following infection or operation in young adults with relatively sound hearts are well treated by quinidine. Results in arteriosclerosis and hypertension are poor. Before using quinidine the clinician must weigh possible benefits to be derived against possible dangers incident to the use of the drug.

A careful selection of patients is essential to successful quinidine therapy. Insistent demand that each candidate have a relatively intact myocardium increases the likelihood of the arrhythmia being adequately controlled. In from 75 to 90 per cent of properly selected and treated cases a regular rhythm is restored and in over 90 per cent of these recurrence of fibrillation will not take place if an individually determined maintenance dose is faithfully continued. Lack of success with quinidine reflects failure to evaluate properly the importance of a relatively sound heart.

**Therapeutic Management**—The patient should be at complete bed rest, in a hospital, under mild sedation and close medical observation. A preliminary assay of the heart muscle is desirable. A ventricular rate above 100 should be lowered by digitalis. Digitalis prevents the occurrence of ventricular tachycardia after quinidine. Heart failure calls for digitalis.

**METHODS OF ADMINISTRATION**—Scored tablets (0.2 gm.) by mouth are most suitable. Vomiting, collapse or coma may preclude oral use of the drug. A soluble preparation for intramuscular use is obtained by the following formula:

	Gm. or cc.
Quinidine hydrochloride	15
Antipyrine	15
Urea	20
Distilled water	to make 100

The mixture is a clear, colorless solution with 0.15 gm. of quinidine hydrochloride in each cubic centimeter. Preparation of this solution is not difficult. The ingredients are readily available. Sterilization is by Berkefeld filter. Storage in stoppered bottles makes it available for emergency use. This, like all quinine solutions, turns brown, but

there is no change of potency or increase in toxicity. An initial dose of 0.45 gm is repeated every two hours according to specifications given below. Pain, local reaction and toxic manifestations are slight. Intravenous quinidine is dangerous and should be employed rarely. A solution is made by vigorously shaking 4 gm of quinidine sulfate in 500 cc of 5 per cent glucose. This is filtered, warmed slightly and given at the rate of 100 cc per hour. Frequent determination of the apical pulse and blood pressure during administration is essential. A sudden drop in blood pressure is best treated by caffeine sodiobenzoate, 0.5 gm intravenously.

**TECHNIC OF DOSAGE**—Of the methods of administration the one described is probably as safe and effective as any. A test dose of 0.2 gm is given the day before treatment is started and the patient is carefully observed by symptoms or signs of idiosyncrasy or cinchonism. The following morning 0.4 gm is given every two hours until (1) regular rhythm at a slow rate is restored,\* or (2) 4 gm of the drug has been given,† or (3) cinchonism, definite and severe, develops, or (4) tachycardia, above 140, occurs, or (5) frequent and persistent extrasystoles presage ventricular fibrillation, or (6) showers of petechiae suggest the imminence of embolism.

Upon restoration of sinus rhythm the next dose is halved (0.2 gm). If the rate remains regular the interval is doubled, i.e., the next half-dose (0.2 gm) is given four hours later. This dosage is continued for the next twenty-four hours, 0.2 gm four times a day, and finally 0.2 gm three times a day before meals, being tried as a temporary ration. Reduction in dosage depends on the condition responsible for the arrhythmia, the total amount required to reestablish normal rhythm, the age and condition of the patient, the state of the myocardium and the urgency of the situation. One may well vary the routine outlined above. When the patient becomes ambulatory the

\* It is essential that a physician, resident or intern, thoroughly acquainted with quinidine therapy, personally determine the apical heart rate before giving the next dose of the drug, an electrocardiogram every two to four hours during therapy, is helpful and, in certain cases, essential.

† Dosage depends on the age, weight and vitality of the patient, on the condition of the myocardium and on the urgency of the situation. A dose of 4 gm is safe for the average individual as is 5 gm for a sturdy patient with a relatively intact myocardium, whereas 3 gm for a frail, ill or aged patient may constitute a large dose. We have rarely used 6 gm., and 8 gm in only one instance. Here it failed to control a rapid ventricular tachycardia in a badly damaged heart in failure following coronary occlusion after digitalis, two previous courses of 5 and 6 gm of quinidine, papaverine, magnesium sulfate and potassium chloride had failed to slow the rate. Digitalis, being resumed, slowed the rate, lessened the decompensation and temporarily increased the patient's comfort.

maintenance dose must be determined again. Provided the underlying disease is not unduly progressive, increased tolerance causes little trouble. A daily ration determined in August 1931 remains adequate in December 1944 without evidence of harmful effects.

A "course" may be repeated two or more times at intervals of a day to a month, depending on the rate of recovery of the heart and the urgency of the situation. More than three attempts are rarely justified and are usually futile.

'Courses' employing smaller dosage and/or longer intervals have not been successful owing to the prompt absorption and rapid excretion of the drug.

### AURICULAR FLUTTER

Less effective here than in fibrillation, quinidine therapy, as previously outlined, has been more effective than digitalis. Some practi-

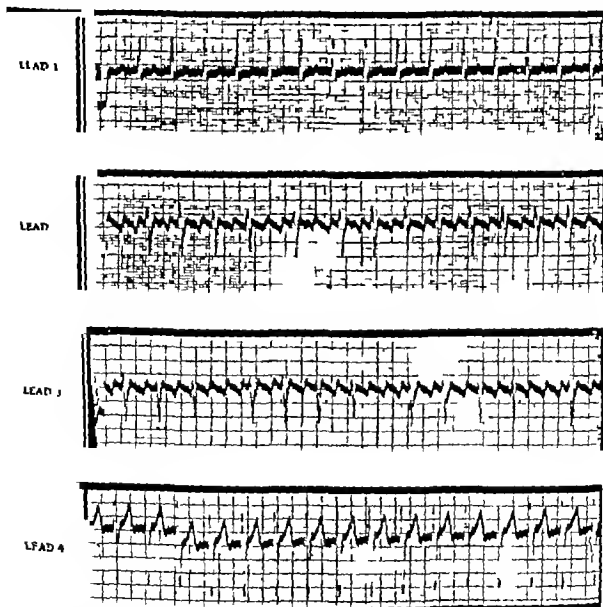


Fig 38—After collapse on February 25, 1939. Auricular flutter with irregular rate and rhythm due to variable A-V block. Note the appearance of Lead I. Chest lead IVR.

tioners reserve quinidine for those who fail to respond to digitalis, but earlier experience has influenced us to use quinidine first and digitalis later. Flutter without failure is best treated with quinidine. With failure digitalis should be used. Quinidine is the initial choice in the treatment of uncomplicated flutter.

*Case History*—A man, aged 48 years, who was first seen on March 24, 1939, with pain in his left chest, shoulder and arm, dyspnea

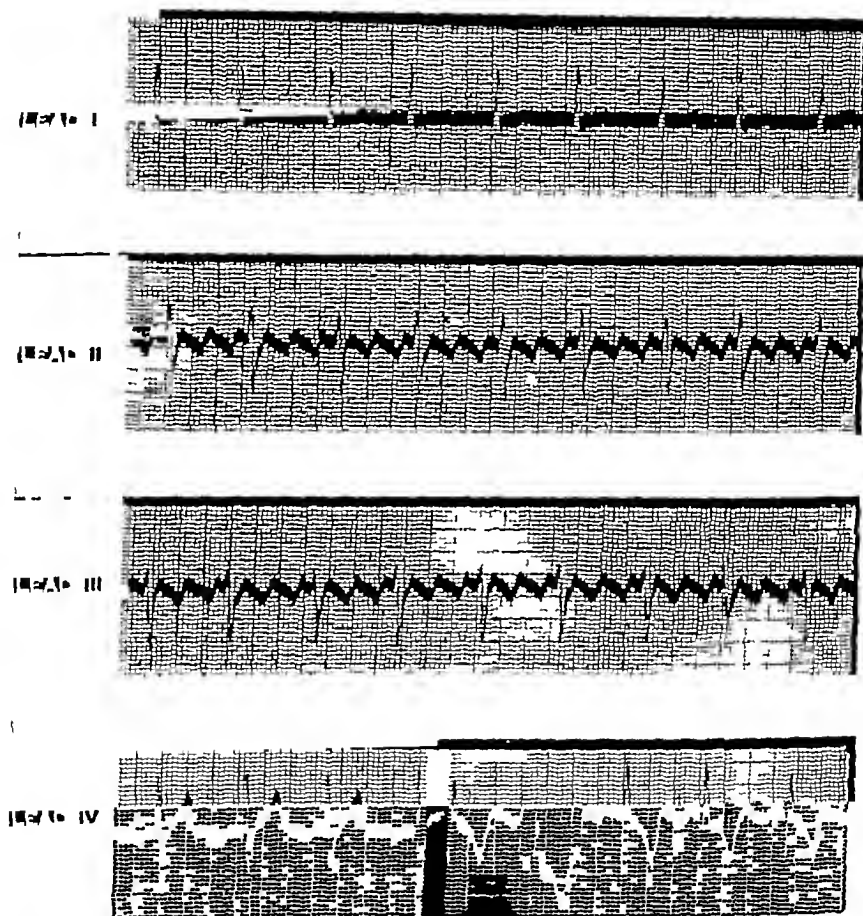


Fig. 39—On examination March 24 Rate auricular 270, ventricular 90 Rhythm regular Chest leads CRIV and V, as in subsequent records

and weakness following "flu" four months previously, had collapsed on February 25, and again on March 17, 1939. Two courses of quinidine, 0.2 gm thrice daily and 0.4 gm four times daily for a week, each had failed to bring relief, and the patient was told that nothing further could be done.

Examination revealed a regular rhythm at a rate of 90 per minute uninfluenced by exercise or vagal stimulation. The blood pressure was 136/84-80. The apex beat was not seen or felt. The heart borders

were within normal limits except for dullness of the lower sternum and prominence of the left auricular area. There was no murmur or thrill and no rales in the lung bases were heard on auscultation. The liver and spleen were not felt and no ascites or ankle edema was present. The blood and urine were negative. X-ray findings were confirmatory. The electrocardiogram revealed an auricular flutter with an auricular rate of 270 and a ventricular rate of 90 per minute, a 3:1 A-V block being present.

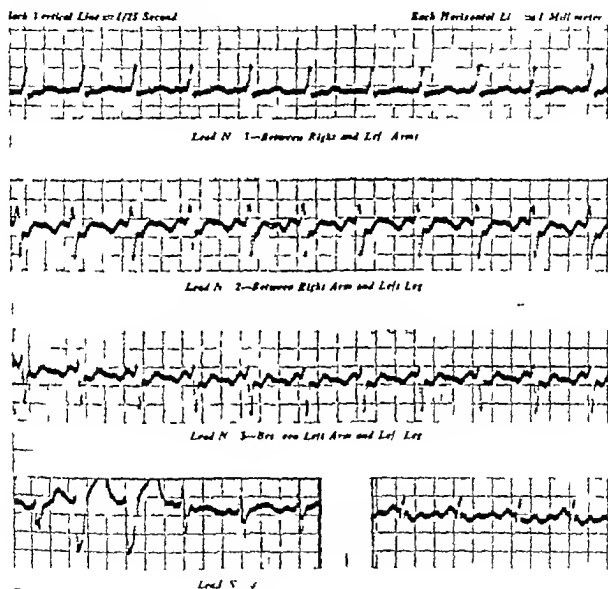


Fig. 40—On March 28, during quinidine therapy

After three days of bromide therapy and rest at home with a test dose of 0.2 gm of quinidine on March 25, the patient entered the hospital on March 27 for treatment. Quinidine sulfate, 0.4 gm was given by mouth at two-hour intervals on March 28 from 8 A.M. to 10 P.M., a total of 3.2 gm. in fourteen hours. The heart rate thereafter was 80 and regular. Quinidine 0.2 gm was given at midnight and this dose was continued every four hours until the patient was discharged on March 30. He continued the drug, 0.2 gm thrice daily. After April 2 he took the same dose twice daily. After September



25 he took one dose of 0.2 gm each morning. Since October 11, 1939, he has reduced this morning dose to 0.1 gm. After hospitalization activity was gradually resumed. He worked part time after three months, full time after six months, as a laborer, and has remained well.

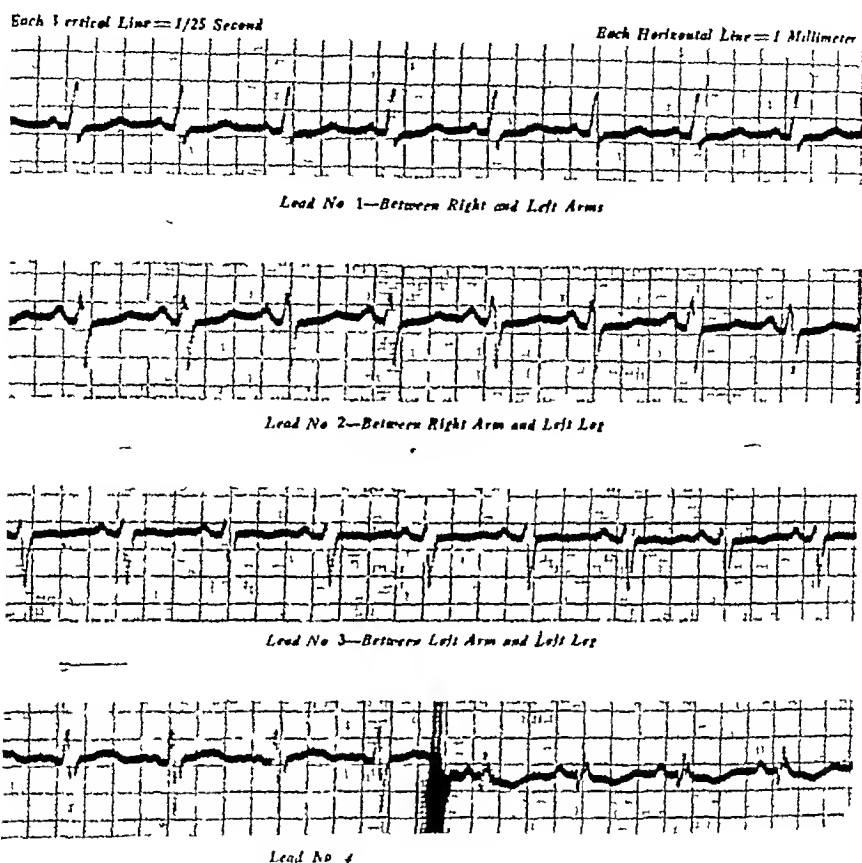


Fig. 41—On March 29, after successful therapy

### PAROXYSMAL TACHYCARDIA

With *auricular* or A-V nodal tachycardia, a younger patient and a relatively sound myocardium, contraindications are fewer. The dosage may be smaller and at longer intervals. Oral administration of 0.2 or 0.4 gm three times a day before meals or four times daily usually relieves these paroxysms. Parenteral therapy is rarely necessary.

Although the condition may occur without preceding or subsequent damage, *ventricular* tachycardia is usually associated with extensive heart disease. In this grave arrhythmia, although the drug is dangerous and may cause fibrillation and death, its action at times is dramatic and life saving. Results are often unsatisfactory. A high mortality is to be expected. If the oral route is not available, intramuscular in-

jection should be used, intravenous medication being reserved for obstinate or moribund cases. Quinidine is toxic and, as mentioned previously, its intravenous use is dangerous and rarely justified.

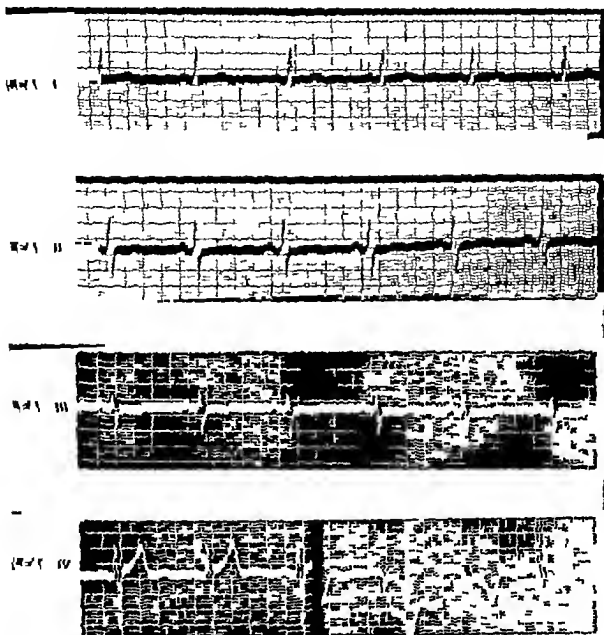


Fig. 42.—On September 25 six months after therapy

#### EXTRASYSTOLES

This arrhythmia if asymptomatic is not an indication for medication. Factors responsible for the extrasystoles should be removed. Relief and/or prevention of recurrences then will be successful in most instances. Quinidine affords relief by decreasing myocardial irritability when this is the basis for extrasystoles. For the ambulatory patient, doses of 0.2 or 0.4 gm. three times a day before meals or four times daily are usually sufficient. The drug may be helpful in overcoming distressing palpitation and heart consciousness and affords reassurance that something can be done should the need arise. Quinidine may control the extrasystoles of digitalis coupling. Digitalis n

quinidine, should be used to control extrasystoles due to heart failure. Rest, bromides, belladonna, strychnine and quinidine, papaverine or digitalis may be preferred or required in certain instances.

### CORONARY OCCLUSION

Quinidine has been advised to reduce myocardial irritability and to lessen the incidence of ventricular tachycardia and fibrillation after infarction. These arrhythmias, following coronary occlusion, are relatively rare. The routine use of a drug, wholly depressant in its action on the myocardium, is not justifiable. Ventricular tachycardia following infarction justifies its use.

### CAUSES OF FAILURE

Usually the lesser action of quinidine is depression of conductivity and the greater effect is prolongation of the refractory period. If the predominant action of the drug is on the refractory period it tends to stop fibrillation. If its effect on conduction predominates, this tends to perpetuate and fix the mechanism. Idiosyncrasy may prevent treatment. Unwarranted fears concerning its dangers may result in inadequate dosage. Toxic symptoms may prevent adequate dosage. Failure is most often the result of improper selection of cases.

### SUMMARY

Quinidine is an ideal drug. It is inexpensive, easily obtainable, promptly absorbed, powerful in action but rapidly excreted and can be given orally or parenterally. It has a high degree of effectiveness combined with relatively low toxicity. It is indicated for the control of certain arrhythmias in relatively sound hearts. It should be given in larger doses at shorter intervals than heretofore. Success with the drug reflects judicious selection of cases. It is a valuable drug if properly used.

### BIBLIOGRAPHY

- Best, C. H. and Taylor, N. B. *The Physiological Basis of Medical Practice*, 2nd ed. Baltimore, The Williams & Wilkins Company, 1940.  
 Carter, J. B. *The Fundamentals of Electrocardiographic Interpretation*, 2nd ed. Springfield, Charles C. Thomas, 1945.  
 Goodman, L. and Gilman, A. *The Pharmacological Basis of Therapeutics*. New York, The Macmillan Company, 1941.  
 Katz, L. N. *Electrocardiography*. Philadelphia, Lea & Febiger, 1941.  
 Sollman, T. *A Manual of Pharmacology*, 6th ed. Philadelphia, W. B. Saunders Company, 1942.

It is to be regretted that, owing to lack of space, the many valuable contributions consulted cannot be included.

## PERNICIOUS ANEMIA

GEORGE E. FARRAR, JR., M.D. \* AND HAROLD L. HYMAN, M.D. †

CLINICAL recognition of primary (Addisonian) pernicious anemia is facilitated by the neurologic and gastrointestinal symptoms which are frequently present. Chronic and mild anemias of the iron deficiency type (hypochromic and microcytic) are often not recognized until an examination of the blood demonstrates a low hemoglobin level. The symptoms of chronic anemia *per se*, occur in other common clinical conditions. Such symptoms are weakness, fatigue, shortness of breath and palpitation on slight exertion, dizziness with exertion or change of posture and mild swelling of the ankles by the end of the day. Pallor is often insufficient to demand attention and may be masked by cosmetics. In the macrocytic anemias the frequently associated stomatitis interferes with the recognition of pallor of the mucous membranes and the slight icterus of the skin and sclerae is confusing especially in artificial light. Conversely pale patients are often found to have essentially normal blood counts, because pallor has other causes than anemia such as edema and myxedema and even more commonly the vascular pallor of the skin which is associated with a great variety of chronic illnesses.

The diagnosis of primary pernicious anemia should be restricted to cases presenting achlorhydria gastrica after the hypodermic injection of histamine, and showing a macrocytic anemia. The patient with pernicious anemia also shows atrophy of the gastric mucosa and often of the tongue, increased numbers of nucleated erythrocytes in the sternal marrow, including more than 2 per cent megaloblasts (nucleus has reticular chromatin and often nucleoli; cytoplasm is deeply basophilic and contains some hemoglobin), a continued need of and response to liver extract and often a history of pernicious anemia in the family. Symptoms may be precipitated by a deficient intake of food (particularly animal protein) due to loss of teeth, change in economic status or food fadism. Patients with only traces of intrinsic

---

From the Department of Medicine, Temple University Medical School and Hospital, Philadelphia

Associate Professor of Medicine Temple University Medical School and Hospital Associate Physician Protestant Episcopal Hospital of Philadelphia

† Resident Instructor in Medicine Temple University Medical School and Hospital Philadelphia

sic factor may remain well as long as large amounts of extrinsic factor are ingested. In the hematology clinic many patients presenting the diagnostic criteria of primary pernicious anemia also show definite evidences of malnutrition, disease of the liver, hypometabolism, etc. The term secondary pernicious anemia often seems appropriate.

#### CLINICAL TYPES OF PERNICIOUS ANEMIA

Minot presented a clarifying analysis of the symptomatology of one hundred patients with pernicious anemia in his private and clinic practice. Patients were divided, according to their symptoms, into four groups as follows:

1 **Gastrointestinal** Thirty-one cases—sore mouth, anorexia, epigastric fullness after meals, constipation, nausea, diarrhea, dyspepsia suggesting peptic ulcer or biliary tract disease.

2 **Neurological** Twenty-six cases—numbness and tingling of the feet and, less often, of the hands, difficulty in walking, stumbling in the dark, urinary incontinence, headache, psychic disturbances.

3 **Generalized or anemic** Thirty-three cases—fatigue, weakness, dyspnea, palpitation, vertigo, usually marked pallor.

4 **Cardiac** Ten cases—angina pectoris, dyspnea, palpitation, edema of the ankles, weakness, usually marked pallor.

Minot noted that symptoms had been present for an average of 2.19 and 1.28 years in groups 1 and 2 respectively before the presence of pernicious anemia was suspected. In contrast, pernicious anemia was diagnosed in less than one year in the anemic and cardiac clinical types.

In general medical work Minot's emphasis on the paresthesias, sore tongue and indigestion is very helpful in the recognition of pernicious anemia.

#### GASTROINTESTINAL

**CASE I**—Miss J. F., aged 71 years, was admitted to the ward with complaints of one year's duration as follows: progressive weakness, epigastric fullness, belching and sometimes nausea and vomiting after meals, anorexia, dyspnea and palpitation after walking one block, swelling of the ankles at the end of the day, dizziness, numbness and tingling of the feet and hands, loss of 40 pounds of weight. Her friends reported that her skin became yellow about one year ago.

Physical examination showed an elderly white woman, whose skin was dry, glossy, thin and lemon-yellow in color. The right eye showed the results of a successful cataract extraction, phthisis bulbi had followed extraction in the left eye. The entire tongue was smooth and shiny. She was wearing false teeth, the gums were in good condition. The heart was enlarged to the left, a loud, blowing systolic murmur.

was heard over the entire precordium. The blood pressure was 120/60. The peripheral arteries felt moderately beaded. The hands were deformed by advanced osteoarthritic changes and there was bilateral hallux valgus with bunions. The patellar reflexes were hyperactive. Both position and vibration sensations were almost absent in the legs. The Romberg test was positive. Pelvic examination revealed only senile changes.

Urinalysis and the serologic test for syphilis gave negative results. Examination of the blood showed hemoglobin 5 gm per 100 cc (33 per cent), red cells 146 million per cu mm, leukocytes 8100, differential leukocyte count, neutrophils 41 per cent (nonfilamented 8 per cent, filamented 33 per cent), lymphocytes 53 per cent, monocytes 5 per cent, eosinophils 1 per cent. The mean corpuscular volume was 123 cubic microns, the color index was 1.18, a modified Price-Jones curve showed 25 per cent of erythrocytes to be less than 7.5 microns in diameter, 17 per cent equal to 7.5, and 58 per cent larger than 7.5 (normally about one third of the cells are in each category). Erythrocytes varied from 3 to 13.5 microns in diameter. X-ray examination showed no abnormality of the gastrointestinal tract with a barium meal, but showed enlargement of the left ventricle and calcification of the aorta in the chest. Gastric analysis after histamine injection showed no free acid.

Ventriculin NNR was administered orally in doses of 10 gm four times a day, in an attempt to assay the potency of a new supply of this defatted hog stomach preparation. The reticulocyte count reached 18 per cent of the red cells on the fifth day of treatment and remained at 18 or 19 per cent for the next four days before decreasing, instead of rising to the peak of about 28 per cent which would be expected from the initial erythrocyte count. The red cell count, however, increased to 2.9 million at the end of two weeks of treatment (see Table 3). It did not rise further after three and four weeks. At this point fever and leukocytosis (white blood cells 16,200, neutrophils 67 per cent) developed. An ischio-rectal abscess was found, incised and drained. The patient was discharged after seven weeks in the hospital with a blood hemoglobin level of 11 gm and an erythrocyte count of 4.5 million.

In the outpatient clinic she received weekly injections of 6 units of liver extract USP for seven months. The red cell count varied between 4 and 5 million and the hemoglobin between 13 and 14 gm and she felt well. During the next three months treatment consisted of 10 gm of ventriculin daily by mouth, the erythrocyte count fell to 3.8 million but it rose in four weeks with parenteral liver therapy to 4.5 million. During this month, gastroscopic examination, performed by Dr. C. L. Jackson, showed atrophic gastritis, the tongue was coated on its posterior third and the anterior third although clean was not red, and both the filiform and the fungiform papillae

appeared normal Parenteral liver extract in doses of 10 units was given three times a month for six months After one and one-half years of treatment the patient was in good general condition for her age She had gained 20 pounds in weight The blood hemoglobin level was 13 gm, the red cells numbered 5 million and the mean corpuscular volume was 84

She remained in good health for two and one-half more years (five years after onset of symptoms) when severe ichthyosis and partial intestinal obstruction, due to inoperable adenocarcinoma of the ovary, developed Pelvic examination had been negative four years before Sternal marrow was aspirated and found to be hyperplastic but not megaloblastic The patient lived another year and a half with one course of x-ray therapy and injections of 30 mg of testosterone propionate three times a week for six months After testosterone was discontinued because there was no objective change in the size of the pelvic tumor, she deteriorated rapidly and died in eight weeks with complete intestinal obstruction at the age of 77 years Autopsy confirmed the diagnosis and disclosed metastases in the liver During the last year of life abdominal cramps after meals caused anorexia and the red cell count did not rise above 3.5 to 4 million in spite of continued parenteral liver therapy (10 units weekly)

**Comment**—It is unusual for patients with pernicious anemia to lose as much weight as 40 pounds, but in spite of this woman's age she regained 20 pounds A poor reticulocyte response and a slow rise in red cell count occurs with oral treatment in a few patients Both infection and senility, as well as poor gastrointestinal absorption, are often associated with an unsatisfactory response to oral therapy The prolonged, submaximal increase in the reticulocyte count indicates an inadequate dose of anti-anemia substance The subsequent failure of oral therapy to maintain this patient's blood count at a normal level is best explained by inadequate intestinal absorption, since parenteral liver therapy was effective even after carcinoma of the ovary appeared

#### NEUROLOGICAL

**CASE II**—Mr W S first came to the Neurology Outpatient Clinic in May, 1939 His complaints had commenced one year before with painful corns on both feet, not relieved by wearing arch supports, and nausea after meals His symptoms included progressive weakness, loss of voluntary control and partial anesthesia of both legs, particularly of the feet, and a loss of equilibrium while standing or walking He found it very difficult to walk without watching his feet, and with his eyes closed or when in the dark he fell During the winter his feet felt very cold to his hands but he was not conscious of their being so cold Increasing sexual impotency had been present for one

and one-half years and lately he had frequently experienced urinary incontinence. Numbness and tingling in his fingers and toes were unpleasant. Poor memory was troublesome at his work as a clerk in a freight yard and he had become irritable, sensitive and antagonistic. Three years previously he fractured his left ankle and was unable to work for eight weeks. Four years previously he lost money gambling and, because of this debt, he was unable to provide for his wife and three children. His wife left him temporarily two years previously and during this period he lost 50 pounds in weight. He had since regained 30 pounds.

TABLE 1—RESULTS OF NEUROLOGICAL EXAMINATIONS IN CASE II

Date	1939		1940	1941	1942	1943
	May	October	October	October	April	May
Gait Ataxia	+++	+	+	+	++	++
Spasticity	+	0	0	0	0	0
Romberg	++	+	++	+	+	++
Position Sense Toes Right	---	--	--	0	0	0
Left	--	0	-	0	0	0
Vibratory Sense Ankles	---	---	---	---	---	---
Wrists	--	-	-	0	0	0
Reflexes Biceps	+++	++	0	0	+	0
Patellar	++	-	-	0	0	+
Achilles	++	---	---	---	-	+
Abdominal	---	0	0	0	0	0
Hoffman	+	+	+	0	0	0
Babinski	+++	++	++	++	++	++

Examination performed by Dr. Sherman F. Gilpin.

Key: + indicates present or, in the case of reflexes, increased; 0 indicates no abnormality; - indicates decreased; --- indicates absent.

Physical examination showed a pale white man appearing his stated age of forty-three years. There was no evidence of acute distress. The tongue was clean, smooth, shiny and pale. Nothing abnormal was found in the chest and abdomen, the blood pressure was 110/80. The neurologic examination is recorded in Table 1. The feet were markedly pronated and the anterior arch was flat. The finger nails were brittle and spoon-shaped (koilonychia).

Urinalysis and the blood Wassermann test gave negative results. Only very small specimens could be obtained on gastric analysis and there was no free acid after histamine stimulation. Anemia was very mild, considering the patient's pallor, and normochromic. Blood count results were hemoglobin 12 gm (71 per cent), red cells 3.6 million,



color index 1, white cells 6450, differential leukocyte count, neutrophils 61 per cent (nonfilamented 7 per cent, filamented 54 per cent), lymphocytes 37 per cent, monocytes 1 per cent, eosinophils 1 per cent. Unexpectedly, the aspirated sternal marrow was hyperplastic and megaloblastic (see Table 2)

TABLE 2—CYTOLOGY OF ASPIRATED STERNAL BONE MARROW IN CASE II

Cell	Per Cent	Normal Range, Per Cent (Osgood)
Granulocytes		
Segmented, Neutrophils	13.5	7-25
Eosinophils	2.5	0-1
Basophils	0	0-0.2
Nonsegmented, Neutrophils	17.0	15-35
Eosinophils	3.5	0-3.6
Basophils	0	0-1
Metamyelocytes, Neutrophils	4.0	1-10
Eosinophils	0.5	0-2
Myelocytes, Neutrophils	1.0	0-10
Promyelocytes	2.5	0-10
Myeloblasts	2.5	0-2
Lymphocytes	5.0	4-16
Monocytes	5.0	0-5
Normoblasts	13.0	2-10
Pronormoblasts	7.5	2-15
Erythroblasts	19.0	0-5
Megaloblasts	3.5	0-0.2
Granulocytes—Nucleated erythrocyte	1.2/1	2/1-9/1

(This marrow film shows a marked increase in nucleated red cells (megaloblasts and erythroblasts) and a slight increase in eosinophilic leukocytes. Two areas of 200 cells each were counted.)

Parenteral liver extract therapy was commenced on June 14 with 60 anti-anemia units USP, this dose was repeated the next day and 20 units were given on June 16 and 17. His legs felt stronger on June 15. Thirty units were then injected intramuscularly every week for two months. On July 12 there was no improvement in symptoms and the blood examination showed a decrease in hemoglobin to 10.5 gm with practically no change in the red count which was 3.55 million. Ferrous sulfate, exsiccated USP X, in doses of 0.2 gm was prescribed three times daily before meals. On August 9 there was still no clinical improvement and, although the blood count was better (hemoglobin 11.5 gm, red cells 4.8 million), anisocytosis was still marked on the blood film. During the next two months, 20 units of liver extract were injected weekly. On October 4 the patient felt generally well, his memory and irritability had improved and he found it less difficult to walk (see Table 1). The laboratory report was almost normal (hemoglobin 12.5 gm, red cells 4.24 million) and an abnormal variation in the size of the erythrocytes was no longer no-

useable. During the next two months the dose of liver was increased to 30 units weekly. On November 19 the blood hemoglobin was 14 gm and the red count 4.9 million. By mid-December, about six months after treatment was started, the patient felt that his symptoms were about 90 per cent relieved. He still experienced difficulty in walking or even standing in the dark and he slapped the forepart of his foot on the floor as he walked.

From December, 1939 to March, 1940 intramuscular injections of 15 units of liver extract were given every two weeks. In February gastric analysis was repeated with histamine stimulation, achylia gastrica persisted unchanged. Since the neurologic findings seemed slightly but definitely worse than in October, 1939 (see Table 1), the dose of liver extract was again increased to an average of 2 units per day—i.e., 30 units every two weeks—which has been maintained every since. Dilute hydrochloric acid USP in a dose of 2 cc. ( $\frac{1}{2}$  teaspoonful) in a full glass of water with breakfast and dinner was prescribed in addition to the ferrous sulfate which the patient had been taking. In May, 1940, the application of metatarsal pads to his shoes alleviated most of the remaining symptoms with his feet. Eleven blood counts between November, 1939 and February, 1944 have shown hemoglobin values between 12.5 and 14.5 gm and red cell counts between 4.41 and 5.1 million. In February, 1941, liver injections were changed from 30 units every two weeks to 60 units of reticulogen (Lilly, 3 cc.) every four weeks. Reticulogen also contains 10 mg of thiamine per cubic centimeter. Symptomatically and to casual observation this man remains cured except for pronated feet and metatarsalgia. Some abnormalities persist in the neurologic examination.

*Comment*—This man illustrates a moderately severe instance of posterolateral column degeneration associated with achylia gastrica but with only a mild, normochromic anemia. Except for the finding of the megaloblastic sternal bone marrow, this case would be classified as an idiopathic combined degeneration of the spinal cord rather than a pernicious anemia. The idiopathic cases do not respond as well to liver therapy and do not show a megaloblastic marrow. It is interesting that this patient experienced severe neurologic disturbances for almost a year without developing sufficient anemia to be recognizable as pernicious anemia. The slowness of the response to liver therapy (three months before any response and six months before marked improvement), the persistence of abnormal neurologic findings, the initial necessity and continuing need for an average of 2 or even more units of liver extract daily parenterally and the diagnostic value of aspirated sternal marrow are illustrated in this patient.

## GENERALIZED OR ANEMIC

CASE III—Miss E. M., aged 70 years, was admitted to the ward in March, 1935, because she was struck by an automobile in front of the hospital. Aside from contusions and fractures of the left fifth to ninth ribs received in the accident her history was as follows. Two years previously her tongue was sore for many weeks. The following spring she experienced dyspnea and weakness on slight exertion as well as a sore tongue. About four weeks before admission these symptoms recurred together with orthopnea, pallor and swelling of the ankles. Bed rest for one week relieved the dyspnea and ankle edema. The other symptoms improved on medication with oral liver extract, iron and hydrochloric acid. Until recent years she had been employed as a practical nurse. She had been living alone in a rooming house and her only support was her old age pension.

Physical examination showed a well-nourished and unusually well-preserved white woman with an icteric pallor. Her tongue had a white coating. A mucopurulent postnasal discharge was visible. The heart and lungs were clear except for the fractured ribs and occasional extrasystoles, the blood pressure was 112/68. Vibratory sensation was impaired in the legs. Fresh retinal hemorrhages and old scars were seen in both eyes.

Urinalysis and the Wassermann and Kahn tests gave negative results. In addition to the fractured ribs, roentgenographic examination revealed spondylolisthesis, osteoarthritis of the spine and osteophytes arising from the inner table of the skull. An electrocardiogram showed only left axis deviation. No free acid was obtained on gastric analysis with histamine. The blood count was hemoglobin 5.8 gm (40 per cent), red cells 2 million, mean corpuscular volume 114. After treatment with intramuscular liver extract, 2 units daily for one week, the reticulocytes increased to 23 per cent on the seventh day, exceeding the average peak of 19 per cent to be expected (see Table 3) from the initial red cell count. With 2 units twice a week, together with 2 cc of dilute hydrochloric acid USP with meals and 2 gm of iron and ammonium citrate USP three times daily by mouth, the hemoglobin had increased to 10.5 gm and the red cell count to 4 million when the patient was discharged from the hospital at the end of seven weeks (see Fig. 1).

She did not return to the clinic for three months and only irregularly thereafter for one and one-quarter years. During these fifteen months she ate liver two or three times a week and received 20 injections of 2 units of liver extract, five erythrocyte counts varied between 4.5 million at three months and 2.6 million after eighteen months. After 20 weekly injections of 2 units, the red cells had increased to 3.8 million and the mean corpuscular volume was 102. When six weekly doses of 6 units each were given the blood picture approached normal, hemoglobin 12 gm, red cells 4.75 million, mean

corpuscular volume 80 During the next fifteen weeks (May-June, July 1937) she came only seven times and received a total of 42 units, the erythrocyte count decreased to 3.9 million and the mean corpuscular volume increased to 90 on this inadequate dosage (average of 0.4 units daily) Weekly doses of 6 to 10 units thereafter maintained normal blood counts Gastroscopy, performed by Dr. Lester Morrison in August 1938 demonstrated atrophic gastritis and the basal metabolism was minus 28 per cent but there was no clinical evidence of myxedema

An episode of acute hemorrhoidal bleeding, corrected by sclerosing injections, occurred in January 1939 and was followed in March by a severe attack of herpes ophthalmicus and months of postherpetic neuralgia In spite of an increase in the dose of liver to 20 units every two weeks the erythrocyte count remained between 3.6 and 4 million Liver was discontinued entirely during August, September and October 1939 and ferrous sulfate 0.2 gm. was used four times daily by mouth, the red cells decreased to 2.9 million with a hemoglobin of 9.5 gm After 10 units of liver extract were injected twice weekly for six weeks the red count increased to 4.5 million While on 10 units weekly and later 30 units every two weeks the red cells varied between 3.5 and 4 million between January and September, 1940 Re-examination by the Cardiac Clinic again revealed no significant abnormalities and the Neurology Clinic reported a normal examination except for the absence of vibratory sensation in the legs, which is common in persons of this age without pernicious anemia The basal metabolic rate was minus 10 per cent and the blood cholesterol 323 mg per 100 cc with 150 mg (46 per cent) in the ester form The patient discontinued taking desiccated thyroid after two days because of nervousness, tachycardia and insomnia During August she experienced severe reactions at the site of liver injections Liver therapy was changed to a horse-liver extract in doses of 7 units weekly intramuscularly and at the end of six weeks the erythrocyte count reached 4.5 million for the first time in ten months Because of a dry skin and pruritus, which she attributed to liver extract, she discontinued treatment and the red count dropped to 3.5 million in six weeks

Parenteral liver therapy was commenced again in June, 1941 In spite of the regular administration of 30 units every two weeks the red count has varied between 3.5 and 4 million (rarely 4.5) with a color index of about 1 The patient is now seventy-nine years old She is in good health with this dose of liver, except for pain associated with osteoarthritis and senile osteoporosis with compression of the bodies of the midthoracic vertebrae

**Comment**—This patient has required continuous use of liver extract. Weakness and a decrease in the erythrocyte count have recurred in about six weeks whenever liver has been discontinued and whenever

the average dose has been less than 1 unit per day (see Fig 43) In general she has been well and active during the eleven years since the onset of her symptoms at the age of sixty-eight years The absence of neurologic or gastrointestinal symptoms of pernicious anemia throughout has been striking In recent years even large doses of liver (30 units every two weeks for nine months) have not maintained an erythrocyte level of 4.5 million per cu mm Perhaps this is explained

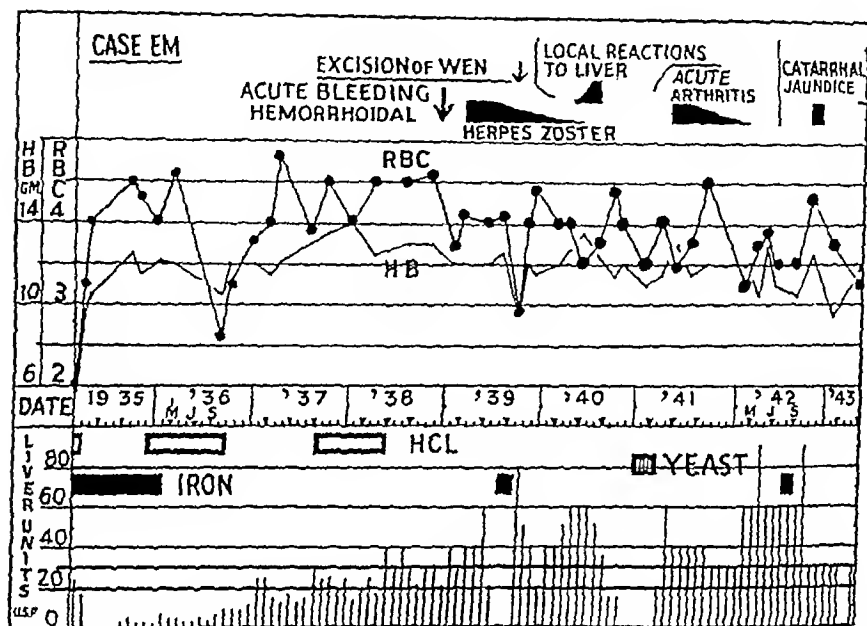


Fig 43—The red blood cell count in millions per cubic millimeter, the hemoglobin in grams per 100 cc of blood and the anti-anemia therapy in Case III during eight of the nine years of observation is presented Intramuscular injections of liver extract are charted in USP units for the preceding four weeks In the date column, the letters indicate March, June and September Important intercurrent events are noted

by the lower normal erythrocyte counts observed in aged persons, but in addition this woman is unable to purchase an adequate diet Her weight has remained between 150 and 160 pounds for nine years, but her diet contains very little meat, egg or dairy products Hydrochloric acid was discontinued after many months because of the abdominal distress and regurgitation after meals which it seemed to cause

#### CARDIAC

**CASE IV**—Mr A Del T was a 56 year old, married native of Puerto Rico For five weeks before admission he had experienced a severe, squeezing substernal pain after exertion This became more frequent and was induced by the slightest activity Numbness of the legs and

fingers was noticed. About three weeks previously, swelling of the ankles and legs, weakness, dyspnea and palpitation on any exertion developed and became progressively worse until he was bedridden. All of his teeth were extracted one week earlier on the advice of a physician. Memory of his early life was almost absent. For several years he had experienced stiffness of his fingers during the winter. Six years ago he had visited the outpatient clinics of this hospital because of a severe generalized dermatitis, no cause was established at that time and a complete blood count showed no abnormality except eosinophilia (white blood cells 5800, eosinophils 19 per cent). He had been employed cleaning railroad passenger cars for many years. He had two adult children.

Physical examination revealed a quiet, middle-aged man lying flat in bed. Weight loss was evident. The skin was light tan in color. His black hair was gray at the temples. The sclerae and mucous membranes of the mouth were icteric. The gums of both the upper and lower jaws had not healed since the recent extractions. The tongue was coated (no redness nor smoothness). The lungs were clear. The heart was not enlarged. A soft systolic murmur was heard over the precordium and in the left axilla. The rhythm was regular, the blood pressure was 100/60. The abdomen was negative. There was massive, soft, pitting edema of both legs, including the thighs. Retinal examination showed pallor and flame-shaped hemorrhages with absorbing centers.

The laboratory reported 3.8 gm of hemoglobin (22.6 per cent) and a red cell count of 1.05 million. The leukocyte count was 3000 with 67 per cent neutrophils (nonfilamented 13 per cent, filamented 51 per cent), 32 per cent lymphocytes, 3 per cent monocytes and 1 per cent eosinophils. The blood film showed 5 nucleated erythrocytes per 100 leukocytes. The mean corpuscular volume was 105. The mean red cell diameter was 11.2 microns (normal 7.4) with a range in size between 4.2 and 16.8. Aspirated sternal bone marrow, examined by Dr. F. W. Konzelmann, showed a predominance of nucleated erythrocytes (megaloblasts and macroblasts) and hypersegmentation of the nuclei of the neutrophilic leukocytes. There was no free acid after histamine stimulation in the gastric juice. An electrocardiogram showed low voltage in Leads I, II and III. Serum cholesterol was 162 mg per 100 cc. (67 per cent in ester form). Total serum protein was 6.87 gm per 100 cc with a normal albumin/globulin ratio. The basal metabolic rate was plus 4 per cent after ten days of liver therapy. The urinalysis was normal. The blood Wassermann was negative.

The patient tolerated an intramuscular injection of 1 cc of liver extract (reticulogen, Lilly). The following day 9 cc was injected (total of 200 units with 100 mg of thiamine hydrochloride). His chest pain disappeared in four days and he was able to be out of bed.

excess of basic requirements in order that a normal condition be maintained and a reserve supply be stored in the body. The amount of effective substance required to produce these results varies considerably in different patients. The condition of the individual patient is the final criterion. Other things being equal, more anti-anemic substance will be required if the patient is old, if he has arteriosclerosis or other disease, or suffers from an infection. In some patients absorption of liver, stomach desiccate, or yeast, given orally, is defective and no adequate response will occur until liver is given parenterally. In others there may be an associated deficiency of iron and a normal state will not be attained until iron is given as well. In patients with changes in the nervous system, complete relief of symptoms may never occur but treatment with large doses of anti-anemic substance must be continued for a long time for, with patience and persistence, some improvement will take place in most cases."\*

**Liver**—The establishment of the anti-anemia unit of liver extract (USP) has brought order out of chaos caused by many preparations with various methods of manufacture. Intramuscular treatment is to be preferred to oral therapy because of greater effectiveness and economy for most patients. When the patient can be taught to give the injections, the cost will not exceed 5 cents per unit. Although by definition, 1 unit USP per day produces a maximum response, it is customary to use larger doses in anemic patients during the first two months. Massive initial doses (see Case IV) have been advocated with the hope of rapidly correcting the tissue deficiency of the anti-anemia factor.

The following program has proved satisfactory for uncomplicated cases in the initial or recurrent stage of relapse: 15 units USP intramuscularly (upper outer quadrant of buttock) daily for three days and then weekly until the erythrocyte count reaches 4.5 to 5 million per cu mm (usually about seven weekly doses). The management of patients with moderate or marked posterolateral sclerosis will be considered below.

For *maintenance therapy*, a dose of 15 units every four weeks is usually adequate. Blood examinations (hemoglobin, red cell count and hematocrit for calculation of the mean corpuscular volume) should be carried out at the end of the third and fourth and the fifth or sixth months of treatment to determine whether this dose is adequate to maintain a normal blood. Subsequently, blood counts at intervals of three to six months are usually sufficient unless symptoms recur or other diseases develop. Patients must understand that this substitution

\* Wintrobe, M. M. Clinical Hematology. Philadelphia, Lea & Febiger, 1942.

therapy must be continued as long as they live. Some cases require 30 or even more units every four weeks. Intercurrent infections or toxemias increase the amount of liver needed. An inadequate diet may be responsible for the large doses required by some patients. Infrequently a poor therapeutic response is associated with local inflammatory reactions at the site of intramuscular injections (see Case III).

*Severe untoward reactions* to intramuscular injections of liver extract are infrequent. Local pain and tenderness, flushing of the upper part of the body and a sensation of faintness are the most common complaints. Less often fever and local induration which persists for days, occur. Injections should be continued because these reactions usually cease after a few weeks. An anaphylactic type of reaction is very rare, however, erythema, urticaria, tachycardia, hypotension, angioneurotic edema and asthma can be terrifying. A hypodermic injection of 0.5 cc of 1:1000 epinephrine hydrochloride solution should be immediately available whenever liver is injected. In some instances it seems probable that the intramuscular injection may have inadvertently entered a small vein. Allergic reactions are more likely to occur after a period of neglected treatment or in patients receiving injections at intervals of two or more weeks. Small doses (0.125 cc) repeated every thirty to sixty minutes will avoid serious reactions. These cases may tolerate small doses three times a week but reactions often recur as soon as the interval between doses is lengthened again. Changing to extract marketed by another manufacturer may not avoid the untoward symptoms. Some evidence suggests that the sensitivity is to some ingredient used in all liver extracts rather than to the animal species of liver. Many commercially available extracts are derived from a mixture of pig and cow livers. An extract prepared from the liver of horses is available and may be useful in some patients. Oral liver extract may be tried but sensitivity reactions may follow ingestion also. The oral use of the dried, defatted gastric mucosa of the pig (ventriculin NNR) in doses of 10 gm, four times a day (or once daily as a maintenance dose), or brewers' yeast powder in doses of 30 to 60 gm daily may solve this therapeutic problem.

**Hydrochloric Acid**—In recent years hydrochloric acid has been neglected in the treatment of pernicious anemia. Some patients never have any gastrointestinal symptoms and many entirely healthy older people have achlorhydria gastrica. In fact, some asymptomatic persons with achlorhydria suffer with indigestion when they take hydrochloric acid with their meals. In many cases of pernicious anemia the gastrointestinal complaints are entirely relieved by the administration of liver extract. Theoretically and from the point of view



of general nutrition over a period of years, it seems desirable to prescribe 2 to 4 cc ( $\frac{1}{2}$  to 1 teaspoonful) of dilute hydrochloric acid USP in a full glass of water or fruit or vegetable juice, to be sipped through a glass straw throughout the course of large meals (not with a sandwich and coffee lunch) in the manner in which some people drink small amounts of water at frequent intervals during a meal. If this large volume of a sour drink is very unpleasant to the patient, the same effect may be obtained at slightly greater expense from 3 to 6 capsules containing 0.5 gm each of glutamic acid hydrochloride, taking half of the capsules before and half after the meal.

**Rest**—Anemic cases are often ambulatory and they may be allowed as much activity as their individual effort limitation will permit. Patients with an erythrocyte count of 1 million per cu mm or less, and those suffering with pneumonia and other infections, congestive heart failure, angina pectoris, etc. should be confined to bed except for periods in a chair two or more times daily to minimize the danger of venous thrombosis and pulmonary congestion.

**Fluid**—Neither limitation nor forcing of fluids is necessary unless demanded by complicating conditions such as infections or cardiovascular disorders.

**Diet**—The needs of most patients with pernicious anemia do not differ from those of other persons of similar age, general health and physical activity. However, since dietary habits are so frequently peculiar, the physician must inquire specifically into the patient's meals and advise, in understandable language, an adequate intake of protein, vitamins and minerals, giving due consideration to the demands of coexistent disorders and to the patient's impressions of the unsuitability of specific foods. Insistence on obtaining satisfactory false teeth for adequate chewing is often important. General dietary instructions are seldom superfluous, the inclusion of milk, vegetables, fruits, eggs, meat or cheese or fish or fowl, whole grain cereal and bread, and butter in the daily diet is usually desirable.

**Vitamins**—An adequate intake of all vitamins in the form of natural foods is always indicated and merits special attention in old people since they often live on a high carbohydrate diet. Unless specific clinical evidences of coexistent avitaminosis are present, the administration of large amounts of the synthetic vitamin fractions is not beneficial and may actually prove deleterious. If the B vitamins are prescribed, a concentrate of a natural material, such as yeast, whole liver, rice bran or wheat germ, is to be preferred to the highly potent but incomplete mixtures of the available crystalline vitamin B factors. In some patients supplementary amounts of vitamin C must be provided.

to obtain a therapeutic response to the exhibition of vitamin B. It has been suggested that the tendency of patients with pernicious anemia to relapse in the spring of the year is associated with a deficiency of vitamin C.

**Iron**—The majority of patients with pernicious anemia do not require the administration of iron. If malnutrition or chronic bleeding has been present, it is desirable to administer iron from the beginning of therapy. Ferrous sulfate, exsiccated U.S.P. X, 0.2 gm. three or four times daily before meals, is cheap, effective and usually well tolerated. If the hemoglobin level does not increase as the erythrocytes approach normal, medicinal iron is indicated.

**Mouth Wash**—Since symptomatic relief of the stomatitis is induced so rapidly by liver extract, local therapy is rarely required. The following prescription is soothing and cleansing.

Sodium bicarbonate,	
Sodium borate,	
Sodium chloride	aa 15 gm.
Oil of peppermint	
Misce.	q.s. flavor

**Sig**  $\frac{1}{2}$  teaspoonful in a glass of warm water as a mouth wash three times a day after meals and at bedtime.

**Transfusion**—This is likewise rarely necessary because of the rapidity of the response to liver therapy. Transfusion of 500 cc. of whole, fresh or bank blood is indicated in patients with erythrocyte counts of less than 1 million per cu. mm. and in patients seriously ill with coexistent infections, such as pneumonia, toxemias, such as uremia and cardiovascular disorders, such as coronary artery disease. If due care is exercised in typing and cross-matching the patient's and the donor's cells and sera and in handling the blood, reactions are no more common than in other diseases. Red cells salvaged from the manufacture of plasma, suspended in normal saline solution and given intravenously within five days of donation are beneficial. In the rare instance of acute hemolytic anemia simulating pernicious anemia, serious hemolytic reactions may occur.

#### MANAGEMENT OF POSTEROLATERAL SCLEROSIS

The patient with pernicious anemia and moderate or marked evidences of degeneration of the posterior and lateral columns of the spinal cord requires more intensive and persistent therapy. The following program is both adequate and practical. Inject 200 units of liver extract U.S.P. intramuscularly during the first week (see Cases II and IV). Then give 50 units weekly until the erythrocyte count

reaches 45 million per cu mm. Continue injections of 30 units every one or two weeks until a satisfactory or apparently maximal (after one to two years) symptomatic relief of the neurological manifestations has been achieved. A permanent maintenance dose of 2 to 3 units daily is indicated. The intramuscular administration of thiamine hydrochloride in doses of about 10 mg three times a week should also be carried out during the first two or three months. The use of the less concentrated liver extracts is favored by some physicians, but the large volume of extract necessary to provide the required number of units of anti-anemia material makes their sole use both uncomfortable and impractical. Furthermore, most of the dilute liver extracts available differ chiefly in water content from the more concentrated preparations produced by the same manufacturers. Satisfactory results are obtainable with the highly concentrated liver extracts (see Case II). Brewers' yeast powder in doses of 30 to 60 gm daily by mouth or the ingestion of  $\frac{1}{2}$  pound of liver several times a week will supply plentiful amounts of all the factors in the vitamin B complex.

A diet high in protein (60 to 80 gm daily with emphasis on animal protein) and carbohydrate (150 to 200 gm daily) is indicated. The injection of insulin in doses of 5 units three times daily before meals for several days has been advocated (Lewy) as a means of rapidly restoring liver function to normal.

Dilute hydrochloric acid should be administered with meals if at all possible. Clinical experience has favored the use of acid in the therapy of posterolateral sclerosis for many years, even before the importance of liver was recognized.

Urinary tract infection must be treated appropriately.

Physical therapy is important to facilitate the recovery of muscle function and coordination. Prescribe heat in the form of a lamp, heating pad or hot water bottle several times daily for periods of about twenty minutes, followed by light stroking massage and active exercise (assisted voluntary motion of involved muscles and joints if necessary). Encouragement, reassurance and help are of great importance. Furniture should be located about the room so that the patient may use the arms to aid himself in walking. The muscle re-education program needed resembles that followed in luetic tabes dorsalis.

#### OTHER MACROCYTIC ANEMIAS

Criticism of the promiscuous use of liver extract in the treatment of any anemic patient without adequate, although simple, diagnostic y has been frequent and is justified. Pernicious anemia requires

continuous treatment for the duration of the patient's life. The rapid symptomatic improvement which follows liver therapy in pernicious anemia eliminates the diagnostic abnormalities of the blood and, without a proven diagnosis, the patient is more likely to neglect treatment. The resultant relapse of pernicious anemia may be associated with irremediable neurologic changes. However, macrocytic anemia occurs in numerous other disorders and liver extract is indicated and valuable, when employed with understanding, in many of these. Whenever a megaloblastic bone marrow is found, liver extract is indicated. When normoblastic marrow exists, liver therapy is not specific but it may be beneficial. In macrocytic, hypochromic anemias iron medication is also indicated.

**Pregnancy**—Among the macrocytic anemias one of the more common is the macrocytic anemia of pregnancy. Iron deficiency (hypochromic-microcytic) anemia is much more common in pregnancy but a macrocytic type occurs not infrequently, especially in malnourished women. Allowing for the physiologic increase in plasma volume which reaches a maximum of about 25 per cent at the sixth month of gestation, macrocytic anemia is characterized by an erythrocyte count of less than 3.5 million, a color index greater than 1.1 and a mean corpuscular volume greater than 97. As is the case in other macrocytic anemias, the variation in size of the erythrocytes is less marked than in primary pernicious anemia, i.e., the diameters are seldom as small as 3 or as large as 16 microns. Leukopenia and paresthesias are unusual. A general dietary deficiency is usually found and liver extract therapy alone is not rapidly and completely effective. A diet containing 50 gm. or more of protein daily in the form of meat, eggs, milk and cheese is necessary.

**Carcinoma of the Stomach**—Macrocytic anemia is not common in this condition but the clinical features may closely simulate pernicious anemia for several years until the condition is inoperable. Among 1014 cases of pernicious anemia at the Mayo Clinic, 17 per cent were found to have cancer of the stomach and 0.39 per cent benign polyps of the stomach. It is a wise clinical practice to make an x-ray examination of the upper gastrointestinal tract of all patients suspected of having pernicious anemia who do not conform to the common constitutional type (blue-eyed blonds with early graying of the hair of the head, sparse body hair and eunuchoid build) or whose gastrointestinal symptoms do not respond promptly to liver therapy. In a patient receiving liver therapy an unexplained change to a hypochromic type of anemia also demands a search for cancer.

**Gastrectomy**.—This procedure, even when the entire stomach is re-

moved, rarely results in macrocytic anemia (none among fourteen total and 460 partial gastrectomies at the Mayo Clinic) but frequently is followed by hypochromic anemia. Since it is now known that the intrinsic factor is formed in the fundal and cardiac portions of the human stomach and since patients rarely survive many years after a total gastrectomy, the rarity of macrocytic anemia is not surprising.

**Intestinal Anastomoses**—Extensive resections of the small intestines, especially where a blind loop of bowel is present, may be followed by very severe macrocytic anemia and usually other manifestations of nutritional deficiency. This anemia usually responds to parenteral liver therapy but much larger doses are necessary than in pernicious anemia (about 50 units weekly). Resection of the blind loop may relieve the macrocytic anemia.

**Malnutrition (Extrinsic Factor Deficiency)**—This condition, unassociated with other manifestations of nutritional deficiency, is rare. The deleterious effect of an inadequate diet on cases of mild or subclinical pernicious anemia has already been mentioned. The important therapeutic measure is the provision of an adequate diet, especially of the extrinsic factor, such as 2 or more ounces of brewers' yeast powder or autolyzed yeast (Vegex) daily. The powder is best administered in a milkshake, Vegex may be mixed with cheese and eaten in a sandwich.

**Liver Disease**—Mild degrees of macrocytosis associated with very slight depressions of the hemoglobin and erythrocytes are frequent in both acute hepatitis and the more chronic cirrhotic disorders of the liver. Some of the increase in size of the erythrocytes may be related to the decreased osmotic pressure of the hypoproteinemic blood plasma commonly present. An actual deficiency in the liver anti-anemia factor may exist. Parenteral liver extract, 10 to 20 units three times a week, is valuable in the general management of patients with disease of the liver.

**Pellagra**—This nutritional deficiency state is usually associated with a hypochromic anemia. Liver extract has long been of recognized value in the treatment of pellagra and is superior to nicotinamide alone, in that liver provides all of the factors of the vitamin B complex.

**Sprue (and Idiopathic Steatorrhea)**—Macrocytic anemia is found in some cases (usually the severe and prolonged ones). Liver extract, 10 to 20 units daily parenterally together with an adequate diet, will correct the anemia and benefit the deficient intestinal absorption in these patients.

**Myxedema**—Macrocytic anemia is less frequent than hypochromic or normochromic anemia in hypothyroidism. When it occurs, cor-

rection of the myxedema with desiccated thyroid is necessary before a full response of the anemia can be obtained with liver extract. A few cases of severe macrocytic anemia associated with pituitary disease have been reported, liver therapy is indicated in such cases.

**Fish Tapeworm (*Diphyllobothrium latum*)**—The possible coincidence of this infestation with primary pernicious anemia has been favored because this tapeworm is most common in the Scandinavian racial group in which pernicious anemia is also frequent. Liver therapy will correct the macrocytic anemia, in some instances the expulsion of the worms has been followed by a reticulocyte response and relief of the anemia without liver therapy.

**Miscellaneous**—Macrocytic anemia exists at times in a number of conditions such as leukemia, myelophthisic anemia, diffuse osteosclerosis, agnogenic myeloid metaplasia of the spleen, aplastic anemia, uremia and may be present several days after an acute massive hemorrhage. In acute hemolytic anemias or hemoglobinurias the macrocytosis may be quite definite, but the marked icterus or dark urine and the severity of the illness avoids confusion with pernicious anemia. Liver extract administered parenterally is often beneficial in serious and chronic infections such as chronic ulcerative colitis, osteomyelitis, etc. and in many conditions in which a parenteral form of vitamin B complex therapy is desired.

#### SUMMARY

Primary pernicious anemia is a disorder involving three systems—neurological, gastrointestinal and hematopoietic.

Paresthesias of the extremities or glossitis and dyspepsia suggest the diagnosis of primary pernicious anemia. Pallor may be absent and even anemia may be very slight. A clean, smooth and pale or red tongue and impaired sense of joint position are the important physical findings.

A diagnosis of primary pernicious anemia requires the laboratory demonstration of a macrocytic anemia and achlorhydria gastrica after histamine stimulation. In questionable cases, sternal aspiration is indicated in search of hyperplastic and megaloblastic marrow.

Treatment consists of adequate intramuscular doses of liver extract, for maintenance an average of  $\frac{1}{2}$  to 3 units U.S.P. daily should be administered for life at intervals of one to six weeks. Patients with combined degeneration of the spinal cord require large doses. Untoward reactions are infrequent. Dilute hydrochloric acid an adequate diet and, in some cases, ferrous sulfate are also important measures. Liver therapy is also valuable in the treatment of some other macrocytic anemias.

## BIBLIOGRAPHY

- Bethell, F H, Sturgis, C C., Hettig, R A and Mallery, O T., Jr Blood, A Review of the Recent Literature Arch Int Med, 71 854, 72 115 and 260 (June, July and August) 1943, 69 856 and 1051 (May and June) 1942
- Cooksey, W B and Horwitz, W H Use of Salvaged Red Cells J.A.M.A., 124 961 (April 1) 1944
- Doehring, P C. and Eusterman, G B Association of Pernicious Anemia and Carcinoma of the Stomach Arch Surg., 45 554 (Oct ) 1942
- Lewy, F. H Vitamin B Deficiency and Nervous Diseases J Nerv & Ment Dis, 89 1 and 174 (Jan and Feb ) 1939
- Minot, G R Some Aspects of the Diagnosis of Pernicious Anemia M CLIN NORTH AMERICA, 18-935, 1935
- Osgood, E E and Ashworth, C. Atlas of Hematology San Francisco, J W Stacey, Inc, 1937
- Wintrobe, M M Clinical Hematology Philadelphia, Lea & Febiger, 1942
- Zillhardt, J C, MacLean, K and Murphy, W P Effect of Thiamine on Residual Neural Disturbances of Treated Pernicious Anemia Ann Int Med, 15 33, 1941

# THE RATIONAL ENDOCRINE THERAPY OF MENSTRUAL DISORDERS

A. L. RAKOFF, M.D.\*

THE increasing number of potent gonadotropic and gonadal hormones has furnished the physician with an array of specific therapeutic agents which can be added to the old stand-bys of rest, diet, emotional readjustment, thyroid extract, and curettage for the treatment of functional menstrual disorders. The brilliant results that are sometimes achieved with these products and their acknowledged biologic potency attest to their potential usefulness, while the disappointing or even untoward results which are not infrequently reported, emphasize the problems and limitations of the treatment of menstrual dysfunctions with sex endocrine preparations. Indeed, it is safe to say that the introduction of hormonal therapy has not simplified the treatment of many gynecologic conditions, but has made apparent to the physician the necessity for a better appreciation of their physiologic basis, the necessity for accurate diagnosis, accurate knowledge of the actions of the hormones and care in their use.

It cannot be overemphasized that menstrual dysfunction is a symptom, not a disease, and may result from a great number of causes. The doctor's first responsibility is to determine whether there are any local organic abnormalities, particularly neoplasms, and then to evaluate the possible influence of the various clinical findings on the physiologic mechanism of menstruation. The need for thorough pelvic examination, and diagnostic curettage when in doubt, is all the more necessary, if endocrine therapy is to be employed in the light of recent warnings<sup>1</sup> that injudicious hormonal treatment may conceal malignancy.

When local and systemic organic disease have been ruled out as factors in disturbances of menstruation the physician still faces a difficult diagnostic problem, for it is frequently not possible to determine from the clinical manifestations the nature of the physiologic disturbance. It may be some dysfunction inherent in the pituitary-ovarian uterine mechanism or it may represent the effects of other

---

From the Departments of Obstetrics and Gynecology, the Endocrine Clinic, and the Endocrine Laboratory, Jefferson Medical College and Hospital, Philadelphia.

\* Director of the Endocrine Laboratory, Jefferson Hospital, Assistant Demonstrator in Obstetrics, Instructor in Gynecology, Jefferson Medical College.



functional abnormalities upon this mechanism, such as dysfunctions of the thyroid, adrenal and other glands of internal secretion, obesity, malnutrition and diseases of metabolism, or emotional and psychic disturbances. In those cases in which these latter causes are discovered and corrected, lasting improvement in the menstrual disorder commonly follows. In a large proportion of the instances, however, some abnormality of pituitary or ovarian function exists for which no exogenous factor can be discovered. It is in this group that sex endocrine therapy finds its most rational application. However, because of their potent biologic actions the sex hormones are not infrequently employed as an adjunct to other types of treatment or to produce some specific effect.

#### DIAGNOSTIC AIDS

The rational use of sex hormone therapy implies the necessity for making an etiologic diagnosis. This is particularly important since many of the clinical manifestations of menstrual dysfunction such as amenorrhea, menorrhagia or irregular bleeding can be associated with various types of sex hormone patterns. Unfortunately, we do not have any simple test for determining pituitary and ovary function. On the other hand, certain diagnostic aids are available. Their proper use has done much to place sex hormone therapy upon a rational basis. The information thus obtained must be interpreted in the light of the normal physiology of the sex endocrine cycle (Fig. 44).

**1. Study of the Endometrium**—Histologic study of the endometrium obtained by curettage is the most prevalent diagnostic procedure employed by the gynecologist. It depicts the end result of the effect of ovarian activity on the endometrium since the last bleeding. Although most commonly employed to rule out local abnormalities of the uterus, or as a therapeutic procedure to control bleeding, from careful histologic study of the tissue one can obtain qualitative evidence of the sum total of estrogenic and progesterone effect. It is particularly useful in determining whether or not there has been a functioning corpus luteum.

Provided that the endometrium is normally responsive, abnormalities of the endometrial pattern can be correlated to a considerable degree with the type of ovarian dysfunction, on the other hand it gives no direct evidence of cyclic variations in the ovary or gonadotropic activity. Whether endometrial biopsies or urine and blood hormone assays afford the better information is a moot point, undoubtedly, together, they afford the most information.

In recent years, endometrial biopsy by suction curettage has been done as an office procedure in suitable cases, namely in patients in

whom there is no suspicion of infection, and in whom the cervix is easily accessible and not too rigid. If properly done, sufficient tissue for adequate examination can be obtained without much discomfort

# THE FEMALE SEX ENDOCRINE CYCLE

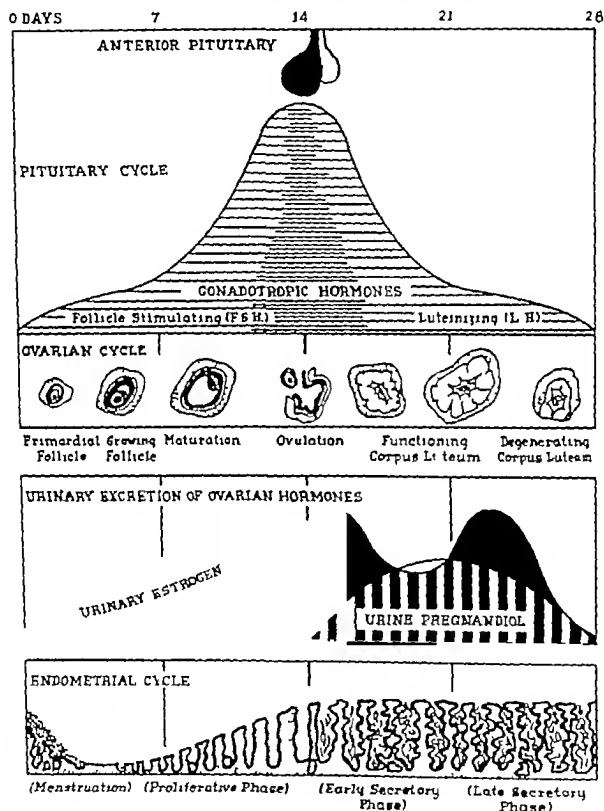


Fig 44

to the patient and at a minimum of time and expense. Those who use the method, however, must thoroughly acquaint themselves with the technic and its possible dangers.

**2. Vaginal Smears**—Cytologic study of the human vaginal epithelium as seen on vaginal smears stained by special methods affords a simple, convenient and inexpensive method for determining estrogenic effect and cyclic ovarian changes. From it, one can easily pick up gross ovarian deficiencies and by observing the day-to-day changes, it is possible to determine fluctuations in estrogenic activity and often the probable date of ovulation.<sup>2</sup> Certain regressive changes are sometimes taken as an indicator of a corpus luteum effect, the accuracy of the latter diagnosis is at present questionable. The effectiveness of therapy can often be easily followed by the vaginal smear method. Considering the amount of useful information which can be obtained for the effort expended, the vaginal smear is not used by the general practitioner or the gynecologist nearly so much as it should be.

**3. Hormone Assays**—Direct determination of the excretion of the gonadotropic and gonadal hormones in the urine yields quantitative data concerning hormonal activity at the time. Although such tests are time-consuming and somewhat expensive, they yield the most direct evidence of endocrine function. Indeed, the biologic gonadotropic assay is the only means we have available for determining gonadotropic activity. This becomes of primary importance in deciding whether a given syndrome is due to a primary ovarian or a primary pituitary dysfunction, and in deciding whether rational gonadotropic therapy is indicated.

The hormones which can be determined in this manner are as follows: (a) Gonadotropic hormone. Biologic assay. (b) Estrogenic hormone. Biologic assay. (c) Progesterone. Clinical determination of its excretion product, pregnandiol (sodium pregnandiol glycuronide). (d) Androgens. Biologic assay can be done but is difficult. Chemical determination of the 17-ketosteroids often reveals comparable information. In the female these are believed to originate in the adrenal cortex.

The diagnostic value of such assays and the normal values of the hormone patterns commonly observed in various dysfunctions have been discussed in more detail in an earlier clinic.<sup>3</sup>

#### PRINCIPLES OF TREATMENT

Specific endocrine therapy of menstrual disorders can be divided broadly into the following categories:

**1. Substitution Therapy**—By this is meant the administration of hormones which directly effect the end organ and for which a deficiency exists in the body. Not infrequently substitution therapy is given in such a fashion in the hope that it will eventually prove to be "stimu-

lation" therapy by giving the "endocrine wheel a spin," such as sometimes happens after substitution therapy for amenorrhea. When substitution therapy is employed the following *disadvantages and limitations* must be borne in mind

(a) When the ovarian hormones are administered for substitution therapy, all hope for ovarian function must be given up for the time being, that is, while large dosages of estrogen are being administered it is not likely that ovulation will occur. This is of particular significance in the treatment of young women who are desirous of pregnancy.

(b) The possibility of inhibiting the pituitary by too vigorous or persistent administration of estrogens must be considered, this is a moot question.

(c) There is considerable evidence pro and con concerning possible deleterious effects of prolonged administration of estrogens and progesterone on the ovary.

(d) The results of substitution therapy cannot be expected to carry over after treatment is discontinued, although sometimes they may.

**2 Stimulation Therapy.**—At the present time, there is no accepted and proven method for stimulating gonadotropic function of the pituitary. Low dosage irradiation to the pituitary or to the pituitary and ovaries has been advocated by a number of workers<sup>4, 5</sup> as a method for the treatment of amenorrhea, anovulatory sterility and various menstrual dysfunctions. It is presumed that the irradiation stimulates the structures treated, but this is open to question. The physiologic effects of this type of therapy are not known nor are the possible harmful effects immediate and remote, although no untoward clinical effects have been reported.<sup>6</sup>

It is believed by many that the cyclic administration of estrogens and progesterone may result in a stimulating "back effect" upon the pituitary. This theory is generally used to explain the continued good results which occur in some cases after substitution therapy has been withdrawn.

The commonest type of direct stimulation therapy is the use of gonadotropic hormones to stimulate the ovary. From the theoretical standpoint, this type of treatment offers many possibilities particularly in the treatment of functional sterility, unfortunately however, gonadotropic therapy presents many difficulties and must still be considered in the stage of clinical trial.

**3 Inhibiting Effects.**—The gonadal hormones are commonly believed to inhibit gonadotropic function of the pituitary, lactogenic hormone and possibly other pituitary hormones. These inhibiting influences

may be employed with benefit in the treatment of certain menstrual dysfunctions

**4 Specific Pharmacologic Effects**—The sex hormones are sometimes administered to produce some specific biologic effect even though their use may be otherwise unphysiologic, thus estrogens may be given to children with gonococcal vulvovaginitis to develop a thick vaginal mucosa and increased vaginal acidity, or androgens may be given to stop functional bleeding by its direct effect on the endometrium. The dangers of this type of treatment are that other undesirable results may be produced, and should usually be employed only as a temporary expedient.

### GONADOTROPIC HORMONES

The following types of gonadotropic hormones for therapeutic use are available

**1 PITUITARY GONADOTROPIC HORMONES**—These are prepared from the pituitary glands of animals, usually sheep, and contain both the follicle stimulating and luteinizing fractions. Because of the difficulties in purification, it is probable that small amounts of other pituitary hormones as well as other proteins are present.

**2 EQUINE GONADOTROPIC HORMONE**—During a short phase of early gestation the pregnant mare produces a gonadotropic hormone which can be recovered in high concentration from the serum, but is not excreted in the urine. Unlike the human chorionic gonadotropin this hormone is rich in the follicle-stimulating as well as luteinizing fraction, indeed in primates its action is chiefly follicle-stimulating.

**3 CHORIONIC GONADOTROPIN**—During human pregnancy the placenta produces huge amounts of a gonadotropic hormone which is entirely luteinizing in its action. Commercial preparations can be conveniently prepared from human pregnancy extracts.

**4 COMBINED PITUITARY AND CHORIONIC GONADOTROPINS ("SYNERGISTIC GONADOTROPINS")**—A commercial preparation\* containing a mixture of chorionic gonadotropin and pituitary gonadotropin is being used on the basis of evidence which indicates that such mixtures have a synergistic effect on the ovary. In rodents greater follicular stimulation and functional activity results from such a combination than would be expected from the additive effects of each alone.

**General Indications**—Gonadotropic therapy is indicated only when there is good clinical or laboratory evidence to indicate a pituitary gonadotropic deficiency. It has been used to stimulate ovarian function whether it be for the correction of the systemic manifestations of hypogonadism, amenorrhea, anovulatory sterility, or functional bleeding. However, it will be readily appreciated that if normal or excessive gonadotropic function is already present these hormones may

\* Synapoidin (Parke-Davis).

exert deleterious effect on the gonads.<sup>7</sup> Furthermore, a "normal" response cannot be expected from diseased or abnormal ovaries and indeed untoward or unpredictable effects may follow under such circumstances. When employed to stimulate the ovaries, every attempt should be made to imitate the normal physiologic pattern for follicular stimulation, no matter which type of preparation is chosen. Injections should be started early in the cycle and continued to the mid-cycle or possibly into the third week, but they should never be given through the entire cycle because of the dangers of producing unruptured follicular cysts, markedly enlarged ovaries or ovarian hemorrhage. Even when given cyclically their administration should not be continued for more than three months without an equal rest period, not only because of the dangers already mentioned but because of the possibility of producing antigonadotropins.<sup>8</sup>

Chorionic gonadotropin is rationally indicated only during the last half of the menstrual cycle and is used to stimulate or maintain corpus luteum function. Chorionic gonadotropin was the first of the gonadotropic hormones to be commercially available and in the early days much was expected from it. Clinical evaluation, however, has proved very disappointing. There has been considerable reason to question whether chorionic gonadotropin exerts any influence at all on the ovary which is not normally stimulated earlier in the cycle. It has also been suggested that under certain circumstances it may produce atretic follicles. Its use in the treatment of menstrual dysfunctions has been disappointing.

Various commercial preparations of chorionic gonadotropin are standardized according to the international standard as adopted by the League of Nations. A similar standard is available for equine gonadotropins but unfortunately a number of the commercial firms have adopted their own units and this has caused much confusion. A similar difficulty exists with regard to the potency of the pituitary gonadotropins. Furthermore it is almost impossible to compare the relative gonadotropic potency of pituitary, equine and "synergistic" gonadotropins, particularly with regard to the human ovary.

The gonadotropic preparations are proteins and are, therefore, capable of inducing local and systemic reactions in sensitive individuals. Local reactions of varying intensity are quite common with all of these preparations but occur less frequently with chorionic gonadotropin. Systemic anaphylactic reactions are most common with the equine gonadotropins, particularly in patients who are sensitive to horse serum. By skin testing or conjunctival testing before injection, hypersensitivity can frequently be detected.

**Amenorrhea**—Gonadotropic stimulation may be tried in amenorrheic patients with gonadotropic failure. Although occasionally such a patient may have other evidences of pituitary deficiency, it is usually not possible to make an etiologic diagnosis except by means of a urinary gonadotropic assay. This type of stimulation is particularly indicated in young women with primary amenorrhea who have failed to undergo sexual maturation. The percentage of successful results with this treatment is not high, particularly if the cases are not properly chosen, but when effective is often more permanent than with substitution therapy, certainly it is a more physiological and rational approach<sup>9, 10</sup>

Any of the follicle-stimulating gonadotropins may be employed for this purpose. The author generally employs the following dosage schemes

1 *Pituitary Gonadotropin*—Fifty to 250 international units intramuscularly two to three times a week for the first two weeks of each month. Repeat for a total of three months. A rest period of at least three months is given before repeating the course.

2 *Equine Gonadotropin*—Same plan as above, employing 200 to 400 I U (or its equivalent) at each dose, intramuscularly.

3 *"Synergistic" Gonadotropin*—Ten to 15 "synergy units" at each injection following the same plan.

**Anovulatory Sterility**.—Gonadotropic hormones find their widest field of application in the treatment of impaired sterility. Unfortunately this kind of therapy is often indiscriminately used in sterile women without adequate study to determine whether there is actual failure of ovulation, let alone determining whether there is a gonadotropic deficiency. Considerable controversy exists as to whether the gonadotropic preparations we now have available are capable of inducing ovulation in the human ovary in the absence of normal pituitary stimulation, and the validity of the clinical experiments which have been performed in this regard have been subjected to much criticism. On the other hand, many conservative workers believe that in properly chosen cases gonadotropic stimulation has afforded the additional "boost" necessary to result in ovulation and successful pregnancy.

The same dosage scheme suggested for the gonadotropins in the treatment of amenorrhea may be employed. On occasion larger dosages or more frequent injections may be given in the second week of the cycle. Also intravenous injection of as much as 2000 I U of equine gonadotropin may be given intravenously on the tenth to the twelfth day of the cycle but this is particularly hazardous not only because of the possibility of severe anaphylactic reaction but because

of marked ovarian enlargement which may follow. We have observed ovarian hemorrhage requiring operation following injudicious therapy of this kind.

**Functional Bleeding**—In some cases of menometrorrhagia, gonadotropic therapy has yielded excellent results and occasionally has succeeded where androgens have failed, in other instances the administration of gonadotropins has been of no use whatsoever. In our experience the patients with low or absent gonadotropins and estrogens are most likely to obtain a good result and will often stop bleeding after two or three injections. In the beginning it is usually necessary to give the injections every second or third day for two to three weeks after which the same dosage schedule given above for the treatment of amenorrhea can be followed.

In young women with functional menorrhagia beneficial results are occasionally obtained with chorionic gonadotropin in dosages of 200 to 300 I U given two to three times weekly during the last two weeks of the cycle.<sup>11</sup>

**Dysmenorrhea**—Follicle-stimulating gonadotropins are usually of no value in the treatment of primary dysmenorrhea. Chorionic gonadotropin given during the last two weeks of the cycle does not often yield favorable results.

### ESTROGENS

**General Indications.**—Estrogenic hormones are logically indicated in those menstrual disorders which are associated with a primary ovarian deficiency. This type of treatment is substitutional in character and, therefore, the results obtained are frequently only of temporary value. Under certain circumstances, however, such substitutional therapy may induce effects which may be quite permanent and quite worthwhile. An example is the induction of sexual maturation with the development of the secondary sex characteristics and growth of the uterus in young women with infantilism due to a primary ovarian deficiency.

Estrogens may also be employed to inhibit the pituitary if there is excessive gonadotropic function as the cause for the menstrual disorder. Primary hypergonadotropism, however, is uncommon. It may be encountered early in basophilic and eosinophilic tumors of the pituitary but usually excessive gonadotropic function is secondary to an ovarian deficiency.

Estrogens are not infrequently employed in the treatment of functional uterine bleeding on an empiric basis, on the theory that estrogens will "build up" the endometrium and thus stop the bleed-



ing Although this may be beneficial in an atrophic type of endometrium, its value in patients with a hyperplastic endometrium is questionable and its use open to criticism

Estrogens also may be employed if given in fairly large doses to inhibit ovulation where this is considered desirable, such as in the treatment of certain types of dysmenorrhea, premenstrual tension and unusual moulmina.

The physician today has a large choice of natural and synthetic estrogens from which he may choose These differ in potency, oral effectiveness, toxic effects and expense It is difficult to evaluate their relative effectiveness, advantages and disadvantages It is therefore best for one who only occasionally uses these hormones to become familiar with a few representative members so that he may better know just what response to expect.

**Amenorrhea and Hypomenorrhea.**—Estrogens are quite commonly used to bring on bleeding in patients with primary or secondary amenorrhea or to “regulate” the periodicity and amount of flow in patients with infrequent or scanty menses Treatment of this type is not always justifiable If history and physical examination including pelvic examination fail to reveal any demonstrable endocrine cause for the trouble, it then becomes necessary to decide whether the deficiency is primarily one of inadequate gonadotropic stimulation, a primary functional disorder of the ovaries, or a uterine defect In the case of a primary ovarian hypofunction, substitution therapy with estrogens or estrogens and progesterone may be attempted<sup>12</sup> This is particularly worthwhile if there are systemic manifestations of hypogonadism On the other hand, if the young woman is normally developed, the induction of bleeding by substitution therapy may be only of psychological benefit, occasionally however, it is true that inducing a number of bleedings by substitution therapy may start normal cycling

If estrogens alone are to be used, the hormone should be given in moderately large dosage by injection (10,000 to 50,000 I U twice weekly) or orally (diethylstilbestrol 0.25 to 1.0 mg daily or its equivalent) for a period of three weeks and then withdrawn Bleeding most commonly occurs about one week following estrogen withdrawal There may, however, be considerable variation depending upon the hormonal status of the individual and their sensitivity to the hormone Occasionally patients will even “break through” with bleeding during the time that the hormone is being administered Under such circumstances, the estrogen is stopped until the flow is over and started again

If no bleeding has occurred within ten days after estrogen is withdrawn, it is usually wise to begin again, possibly with a higher dosage. If no bleeding can be induced by the cyclic administration of estrogens alone, the addition of large doses of progesterone (see below) during the last few days of treatment may be beneficial. Failure to obtain success after a reasonable trial on substitution therapy, justifies further investigation including diagnostic curettage.

**Sterility**—It must be remembered that the administration of estrogens is not rational therapy for the treatment of sterility. It may be used as a temporary device for the treatment of associated hypoplasia of the uterus or amenorrhea if the latter are due to an ovarian deficiency. During the course of estrogen administration, if large dosages are being employed, it is probable that any attempt at ovulation will be inhibited. Also to be considered are the possibility that the prolonged administration of estrogens may inhibit the pituitary or ovary or both for sometime, although as already stated this is a debatable point.

**Functional Bleeding**—It is believed that most types of functional uterine bleeding are due to some abnormality in the cyclic production of estrogens or in their metabolism. During the normal menstrual cycle, estrogens rise progressively during the follicular phase to reach a peak shortly after ovulation (Fig 44). This is followed by a fall for several days and then a second rise as the corpus luteum becomes functionally active. This second peak is reached about five or six days before the expected menses and then is followed by an abrupt fall which is believed to precipitate bleeding. Any condition which will result in an irregular estrogen curve may produce abnormal bleeding.

From this standpoint, the continued administration of high dosages of estrogen should prove useful in controlling bleeding and indeed, this is clinically often the case. It is also often of benefit in controlling the postovulatory bleeding which occurs in some women. However, this type of treatment can hardly be said to correct the underlying defect in all or even most types of functional bleeding. It is most helpful in the treatment of bleeding associated with an atrophic endometrium in young women when the latter is due to a primary ovarian defect. If, on the other hand, the bleeding occurs from a hyperplastic endometrium, then the administration of more estrogen may precipitate more troublesome bleeding at a later date. This applies also to all types of bleeding associated with high estrogen levels or prolonged production of normal estrogen concentrations such as may be encountered with follicular cysts, corpus luteum cysts and that clinical syndrome known as "metropathia haemorrhagica".

This author particularly disapproves of the use of enormous dosages<sup>18</sup> of estrogens as a device to stop bleeding of any etiology even though it may be used only as a temporary measure. Until more is known concerning the direct and remote effects of such large dosages of estrogenic hormones upon human physiology, this type of therapy should be considered only from the standpoint of clinical investigation. Moreover, its possibilities in obscuring the etiology of the bleeding are particularly dangerous.

**Dysmenorrhea.**—It is well known that dysmenorrhea is relatively uncommon in anovulatory cycles. On this basis, the administration of sufficient estrogen to inhibit ovulation has proved to be dramatically successful in a large percentage of cases. However, the benefit thus derived does not usually continue after hormonal treatment has been stopped. For this reason it is questionable whether one is justified in employing it for more than two or three months at a time, if that long, until we know more about the ultimate effects of the continued uses of estrogens. Where such treatment is to be employed the estrogen is started on about the fifth day of the cycle in a dosage of 0.5 to 1.0 mg of stilbestrol daily or its equivalent. It is continued until the twenty-first day of the cycle. In cycles in which ovulation has been inhibited by this means, there is frequently a marked reduction in associated symptoms of premenstrual tension, migraine, depression, and occasionally in more unusual manifestations which may be associated with the menstrual phase such as purpura, ulcerations of various mucous membrane, marked edema, and the like.

**Contraindications.**—There can be no question whatsoever that the indiscriminate and injudicious uses of the estrogens has resulted in a marked increase in gynecologic disorders.<sup>1</sup> This is partly due to the fact that these potent hormones are often being employed without proper diagnostic investigation, without adequate pelvic examination at frequent intervals and without adequate supervision. In the treatment of menstrual disorders particularly, estrogens should not be employed for treatment until every reasonable effort to exclude neoplasm or other local organic factors as a cause has been made. Very frequently, particularly in the age group beyond 30, this will involve in addition to careful pelvic examination, a diagnostic curettage. Although it has never been proved that estrogens are carcinogenic for the human, the fact that they stimulate certain types of cancers in lower animals raises the question as to whether it is wise to employ estrogens in women with family histories of genital or breast malignancies.

Prolonged use of estrogens in young fertile women is to be dis-

couraged because of possible inhibiting effects upon the ovary and pituitary. The unphysiologic or contraphysiologic use of estrogens frequently results in further disruption of the menstrual cycle and other unfavorable effects.

Some women may exhibit symptoms of toxicity, particularly nausea, headache and general malaise, following the use of the synthetic estrogens. Occasionally, patients may note an allergy to the oil in which the hormone is dissolved, or develop small lipomas at the sites of injection.

Finally, it must be emphasized that estrogens should be given cautiously to women for the treatment of the menopausal syndrome and only when really required. Every effort should be made to keep the dosage below that which might result in uterine bleeding. Once bleeding has started, the responsibility for differentiating between malignancy and estrogen withdrawal bleeding belongs to the physician, and not infrequently presents a very confusing problem.

#### PROGESTERONE

**General Indications**—Progesterone, the hormone of the corpus luteum, acts upon the endometrium which has been primed by estrogen during the follicular phase to produce a secretory or pregravid endometrium. If pregnancy does not occur the corpus luteum degenerates with a failure of estrogen and progesterone and consequent menstruation. If pregnancy does occur, progesterone acts as a "uterine sedative." It is also necessary for the normal metabolism of the estrogens.<sup>14</sup>

The early clinical results with progesterone in the treatment of functional bleeding, dysmenorrhea and threatened abortion were rather disappointing. Today with the availability of larger dosages of the synthetic hormone and a better understanding of its action, progesterone has a very definite but not too large field of application in the treatment of menstrual disorders. It is also now quite popular as an aid in the treatment of amenorrhea, since Zondek<sup>9</sup> has shown that bleeding will occur within a few days following the administration of large dosages of progesterone to an estrogen-primed endometrium. Smaller dosages of progesterone usually delay menstruation. It is also becoming increasingly apparent that in order to obtain the typical progesterone response in the treatment of corpus luteum deficiencies in the non-pregnant or in the pregnant woman, it is frequently necessary to give it with an adequate amount of added estrogen.

**Amenorrhea**—Secondary amenorrheas of functional origin which are

of less than six months' duration will almost invariably respond with bleeding within three days after the administration of 40 to 60 mg of progesterone if injected over a period of two to five days (Zondek<sup>15</sup>). Usually we give the hormone in three equal daily injections. Some patients with amenorrhea up to two years of duration may respond similarly. In amenorrheas of longer duration and also in primary amenorrheas it is usually necessary to prime the patient first by giving moderately large dosages of estrogen for one to three weeks before giving the progesterone, or the estrogen may be given simultaneously with the progesterone. As shown by Zondek,<sup>15</sup> the use of alpha-estradiol 0.5 to 1.0 mg given together in the same syringe with progesterone 10 mg daily for five days works very well in these cases.

For oral therapy diethylstilbestrol 0.5 to 1.0 mg may be given daily for five days to two weeks followed by anhydro-hydroxy-progesterone (pregneninolone) 60 to 80 mg daily for five days. The results are sometimes not quite as good as by injection.

Large dose progesterone, or progesterone and estrogen treatment has in our experience resulted in bleeding in patients with either primary ovarian or gonadotropic deficiencies. After inducing this type of bleeding for three consecutive months a considerable proportion of the patients will have one to three spontaneous "periods." A small proportion will continue to menstruate regularly for a longer period of time during which pregnancy may occur.

**Functional Bleeding**—Intermenstrual bleeding occurring in anovulatory cycles will usually respond to the administration of moderate dosages of estrogen and progesterone given from the tenth to the twenty-fifth days of the cycle. However, equally good results are usually obtained with estrogens alone. In menorrhagia associated with a hyperplastic endometrium (so-called "hyper-hormonal" bleeding), especially if the cycle has been delayed, the administration of progesterone 5 mg twice a week during the last two weeks may be helpful. In other types of functional bleeding the use of progesterone is not of consistent help.

**Early Miscarriage**—Some patients are believed to abort because of the failure of the corpus luteum. Where this is suspected we have found it helpful to start such patients on full substitution therapy as soon as pregnancy is suspected. We give progesterone 10 mg three times weekly with estradiol 10,000 rat units at the same time or diethylstilbestrol 1 to 2 mg orally daily. This treatment is continued until the sixteenth week of gestation and is then gradually withdrawn. In many instances we gradually increase the stilbestrol to 5 mg daily. We have never experienced any untoward results from this type of

treatment and have been able to carry to term a number of habitual aborters, some of whom miscarried previously on progesterone alone (without estrogen). Karnaky<sup>16</sup> has reported good results with estrogen alone.

**Dysmenorrhea**—Progesterone is commonly given a therapeutic trial in patients with dysmenorrhea on the assumption that as a uterine "sedative" it will lessen uterine cramps. The results in such cases are usually quite disappointing and not infrequently the dysmenorrhea is made more intense. This is not surprising when we recall that the majority of patients with dysmenorrhea have normal ovulatory cycles and therefore do not have a corpus luteum deficiency, furthermore the inhibition of the corpus luteum phase by the administration of large dosages of estrogens early in the cycle not infrequently results in a painless period. Until more is known concerning the factors underlying dysmenorrhea, it is doubtful that endocrine therapy will be wholly successful.

#### ANDROGENS (TESTOSTERONE)

**General Indications**—Although the female adult excretes almost as much androgenic hormones as the male the sources, i. e., the precursors of these in the female are imperfectly known, and concerning their influence on normal menstrual physiology we can at present only conjecture. Despite this the male sex hormone, testosterone, has proved to be a potent gynecologic weapon, and it would indeed be of inestimable value if it were not for the undesirable masculinizing effects which limit its use. Testosterone has an "anti-estrogen" effect by virtue of the fact that it tends to neutralize or overcome some of the effects of estrogens on the end organs including the endometrium, myometrium, vaginal and cervical epithelium and breasts, and also because it inhibits the gonadotropic function of the pituitary. Testosterone is also believed by some to have a direct effect on the blood vessels of endometrium, and by others to exert a progesterone-like effect on the myometrium. Whether testosterone exerts any direct effect upon the ovary is a moot point.

The masculinizing effects of testosterone generally appear in the following sequence, oiliness of the skin and scalp, acne, hirsutism of face, then of chest, then of abdomen and limbs, deepening of the voice, and enlargement of the clitoris. The oiliness of the skin and acne generally disappear soon after the medication is stopped. Hirsutism may slowly regress but not uncommonly persists and rarely continues to become worse after the hormone is withdrawn. Deepening of the voice regresses only very slowly and singers generally

complain that the original pitch does not return, enlargement of the clitoris, if it occurs, is particularly likely to persist

In the treatment of gynecologic disorders<sup>17, 18, 19</sup> testosterone is most commonly used for its inhibiting effect on the endometrium in the treatment of various types of functional bleeding, and more recently in the treatment of endometriosis<sup>20</sup> Like the estrogens it can be used to inhibit the pituitary for the treatment of the menopausal syndrome in those cases in which estrogens are contraindicated, although the clinical results are not nearly so effective It may also be used to inhibit lactation in the puerperium, exerting its influence both on the pituitary and the breasts

**Functional Bleeding**—Testosterone may be used as a palliative measure in all types of functional bleeding, but since its effect is to produce an atrophic endometrium it is apparent that it is often not the most physiologic choice and has the added disadvantage of undesirable side effects In *functional* bleeding at the menopause (as proved by diagnostic curettage) androgens may be particularly indicated because fertility is no longer desired Testosterone propionate can be given by injection in dosages of 25 mg two or three times weekly until the bleeding stops, after which the dosage may be cut to 10 mg twice a week until there is no tendency for recurrence of bleeding Methyl testosterone may be given orally, but five times the dosage is required It is particularly useful for "maintenance" therapy in dosage of 5 to 10 mg daily until it can entirely be withdrawn In order to avoid hirsutism it is generally agreed that the dosage should be kept under 300 mg of testosterone propionate per month (25 mg three times weekly) A much safer rule is to begin cutting the dosage as soon as acne appears, regardless of the amount being given, since some women are particularly sensitive to the masculinizing effect If this type of bleeding is not promptly and effectively controlled by small or moderate dosages of testosterone, the use of radium or surgery if indicated is generally preferred

Most cases of severe pubertal bleeding respond better to androgen therapy than to other types of endocrine treatment. This syndrome is generally characterized by high gonadotropin and low or moderate estrogen values, the endometrium may be hyperplastic or atrophic The administration of estrogens or progesterone is sometimes beneficial but not infrequently they precipitate further bleeding During the first week of treatment as much as 150 mg of testosterone may be required to control the bleeding, thereafter the dosage can be reduced For the first several months it is usually necessary to continue with 30 to 50 mg a week, then 10 mg of methyl testosterone daily

by mouth during the last two weeks of each cycle including the bleeding phase, and then 10 mg only during the period of flow, until finally the hormone can be entirely withdrawn. If an excess of testosterone is given it is not uncommon for the period to be delayed as much as a month or more.

**Dysmenorrhea.**—Testosterone is believed by some to have a relaxing effect on the myometrium and has therefore been employed for the treatment of dysmenorrhea. We have obtained favorable results in only a moderate proportion of patients thus treated. The dosage suggested is 10 to 25 mg of testosterone propionate twice a week during the last two weeks of the cycle or 5 to 10 mg of methyl testosterone orally from the fifteenth to the twenty-fifth days of the cycle. Such therapy should not be used indefinitely because of possible accumulative arrhenomimetic effects.

#### BIBLIOGRAPHY

- 1 Scheffey, Lewis C. and Farrell, David M. The Role of Injudicious Hormonal Therapy in the Delayed Diagnosis of Uterine Cancer. Read at the Ninety fourth Annual Session of the Scientific Assembly of the American Medical Association, June 12-16, 1944, Chicago, Ill.
2. Rubenstein, B. B. The Vaginal Smear—Basal Body Temperature Technic and Its Application to the Study of Functional Sterility in Women. *Endocrinology*, 27 843, 1940
- 3 Rakoff, A. E. The Diagnostic Value of Hormone Assays. *M. CLIN NORTH AMERICA*, 26 1915 1942.
- 4 Mazer, Charles and Greenberg, Rose. Low Dosage Irradiation in the Treatment of Amenorrhea. *Am. J. Obst. & Gynec.*, 46 648 1943
- 5 Mazer, C. and Israel, L. S., Diagnosis and Treatment of Menstrual Disorders and Sterility. New York, Paul B. Hoeber Inc., 1941
6. Kotz, J., Elward, Joseph F. and Parker, Elizabeth. Non harmful Effects of Irradiation of the Pituitary Region of Rabbits. *Am. J. Roentgenol.*, 46 543 1941.
- 7 Davis, Edward M. and Hellbaum, Arthur A., Present Status of Gonadotropic Therapy in Gynecologic Practice. *J. Clin. Endocrinol.*, 3 517, 1943
- 8 Leatham, James H. and Abarbanel, A. R. The Problem of Antagonistic (Antigonadotropic?) Substances to Equine Gonadotropin in Clinical Therapy. *West. J. Surg., Obst. & Gynec.*, 51 177 1943
- 9 Rydberg, Erik and Pedersen Bjergaard, K. Effect of Serum Gonadotropin and Chorionic Gonadotropin on the Human Ovary. *J.A.M.A.*, 121 1117 1943
- 10 Hamblen, E. C. Endocrine Therapy in Gynecology and Obstetrics. *Am. J. Obst. & Gynec.*, 45 147 1943
- 11 Vogt, William H., Jr. and Sexton, Daniel L. Treatment of Menstrual Disorders with Pregnant Mares Serum. *Am. J. Obst. & Gynec.*, 42 81, 1941
- 12 Smith, George Van S. The Present Status of Hormone Therapy in Gynecology. *M. CLIN NORTH AMERICA*, 27 1373 1943
- 13 Karnaky, Karl John. Dysfunctional Uterine Bleeding. *J. Clin. Endocrinol.*, 3 648 1943
- 14 Corner, George W. Corpus Luteum Hormone. Glandular Physiology and Therapy. American Medical Association Chicago 1942, p 115



- 15 Zondek, Bernhard Simplified Hormonal Treatment of Amenorrhea  
J.A.M.A , 118.705, 1942
- 16 Karnaky, Karl John Preliminary Report. South M J., 35 838, 1942
- 17 Geist, Samuel H Androgen Therapy in the Human Female J Clin Endocrinol., 1 154, 1941
- 18 Salmon, Udall J Rationale for Androgen Therapy in Gynecology J Clin Endocrinol., 1 162, 1941
- 19 Hamblen, E C Rationale of Androgenic Therapy in Gynecology J Clin Endocrinol., 1 180, 1941
- 20 Hirst, J C Favorable Response of Advanced Endometriosis to Testosterone Propionate Therapy Am J Obst. & Gynec , 46-97, 1943

# CUMULATIVE INDEX

- ABORTION, early, progesterone in *Jan* 264  
 Albuminocytologic dissociation in acute infectious radiculoneuritis, *Jan.*, 1  
 Alcohol injections for facial pain, *Jan.*, 77  
 Alcoholism criminal responsibility and *Jan* 212  
 Amenorrhea hormone therapy *Jan.*, 258 260 263  
 Androgens in menstrual disorders, *Jan* 265  
 Anemia pernicious, *Jan* 229  
     clinical types, *Jan* 230  
     liver therapy *Jan.*, 242  
     posterolateral sclerosis in management *Jan* 245  
 Anemias macrocytic, *Jan.*, 246  
 Ankle clonus in pyramidal tract lesions, *Jan.*, 56  
 Arrhythmias, quinidine in *Jan*, 216  
 Auricular fibrillation quinidine in *Jan.*, 217  
     flutter quinidine in, *Jan.*, 223  
 Axillary nerve injuries, *Jan*, 23  
  
 BABINSKI sign in pyramidal tract lesions *Jan*, 47  
 Behavior Clinic of criminal court *Jan* 202  
 Biopsy endometrial *Jan.*, 252  
 Brachial plexus injuries, *Jan* 19  
  
 CAUSALGIA, *Jan.*, 13  
 Chaddock's sign in pyramidal tract lesions *Jan* 50  
 Chordotomy for intractable pain *Jan* 98  
 Choriomeningitis lymphocytic, benign *Jan* 36  
 Circus movement, *Jan.*, 216  
 Clawed hand in ulnar nerve injury *Jan.*, 15  
 Clonus in pyramidal tract lesions, *Jan* 56  
 Coronary occlusion, quinidine in *Jan* 227  
 Criminal responsibility, epilepsy and *Jan.*, 212  
     insanity and *Jan* 195  
     mental retardation and *Jan* 208  
 Curare test for myasthenia gravis, *Jan.*, 129  
  
 DEMENTIA praecox, *Jan*, 148  
 Diet in pernicious anemia, *Jan* 244  
 Drop wrist in radial nerve injury, *Jan* 10  
 Dysmenorrhea, hormone therapy *Jan* 259 262, 265, 267  
  
 ELECTRODIAGNOSIS in peripheral nerve injuries, *Jan*, 23  
 Electroshock therapy in psychoses with insomnia, *Jan* 192  
     outpatient, in psychiatric disorders *Jan* 165  
 Encephalo myelo radiculoneuritis, acute *Jan.*, 1  
 Endocrine therapy in menstrual disorders, *Jan.*, 251  
 Endometrial biopsy, *Jan.*, 252  
 Ephedrine in myasthenia gravis *Jan* 134  
 Epilepsy, criminal responsibility and *Jan.*, 212  
 Erb's paralysis in brachial plexus injuries *Jan* 19  
 Estrogen therapy in menstrual disorders, *Jan.*, 259  
 Extrasystoles, quinidine in *Jan* 227  
  
 FACIAL pain neoplasia as cause *Jan* 91  
     relief of, *Jan.*, 73  
     symptomatic, *Jan.*, 87  
 Feeble-mindedness, criminal responsibility and *Jan.*, 208  
 Femoral nerve injuries, *Jan* 23  
 Ferrous carbonate in facial pain *Jan* 77  
  
 GLYCINE in myasthenia gravis *Jan.*, 135  
 Gonadotrophin therapy in menstrual disorders, *Jan.*, 256  
 Gonda sign in pyramidal tract lesions *Jan.*, 57  
 Gordon's sign in pyramidal tract lesions *Jan.*, 53  
 Grafts, nerve *Jan.*, 27  
 Guanidine in myasthenia gravis *Jan* 134  
 Guillain Barré syndrome, *Jan* 1  
  
 HEART disease, quinidine in *Jan.*, 215  
 Hematoma subdural *Jan.*, 62  
 Herniation of intervertebral disk *Jan* 111

- Hoffman sign in pyramidal tract lesions, *Jan*, 54
- Hormone assays, *Jan*, 254
- Hydrochloric acid in pernicious anemia, *Jan*, 243
- Hypnotics in insomnia, *Jan*, 187
- Hypomenorrhea, hormone therapy, *Jan*, 260
- INJURIES, peripheral nerves, *Jan*, 9
- Insanity and the criminal, *Jan*, 195  
     legal conceptions, *Jan*, 204  
     malingering and, *Jan*, 205
- Insomnia, *Jan*, 178  
     causes of, *Jan*, 180  
     clinical effects, *Jan*, 181  
     general management, *Jan*, 184  
     hypnotics in, *Jan*, 187  
     psychotherapy, *Jan*, 186  
     shock therapy in psychotic cases, *Jan*, 192
- Insulin shock therapy in psychoses with insomnia, *Jan*, 192
- Intervertebral disk, protrusion of, *Jan*, 111
- JOLLY's myasthenic reaction, *Jan*, 129
- KLUMPKER's paralysis in brachial plexus injuries, *Jan*, 19
- LIVER therapy in pernicious anemia, *Jan*, 242
- Lymphocytic chorion meningitis, benign, *Jan*, 36
- MALINGERING of insanity to escape criminal responsibility, *Jan*, 205
- Median nerve injuries, *Jan*, 11
- Median-ulnar nerve injuries, *Jan*, 18
- Medullary tractotomy for facial pain, *Jan*, 84
- Meningitis, lymphocytic, benign, *Jan*, 36
- Menorrhagia, hormone therapy, *Jan*, 259, 261, 264, 266
- Menstruation, disorders of, diagnostic aids, *Jan*, 252  
     endocrine therapy, *Jan*, 251
- Mental disease, criminal responsibility and, *Jan*, 195  
     retardation, criminal responsibility and, *Jan*, 208
- Miscarriage See *Abortion*
- Mouth wash in pernicious anemia, *Jan*, 245
- Musculocutaneous nerve injuries, *Jan*, 23
- Myasthenia gravis, diagnostic tests, *Jan*, 128  
     management, *Jan*, 126, 129
- Myasthenic reaction of Jolly, *Jan*, 129
- NERVE grafts, *Jan*, 27
- Nerves, peripheral, injuries, diagnosis and surgical treatment, *Jan*, 9
- Nervous disease, organic origin in apparent functional cases, *Jan*, 30
- Neuralgia, trigeminal, *Jan*, 73  
     atypical, *Jan*, 85  
     symptomatic, *Jan*, 75
- Neuropsychiatric diseases, symposium on, *Jan*, 1
- Neurotomy, retrogasserian, classical, for facial pain, *Jan*, 80  
     posterior, for facial pain, *Jan*, 83
- ONEIROPHRENIA, *Jan*, 162
- Oppenheim's sign in pyramidal tract lesions, *Jan*, 52
- Organic origin of apparent functional nervous disease, *Jan*, 30
- PAIN, facial, neoplasia as cause, *Jan*, 91  
     relief of, *Jan*, 73  
     symptomatic, *Jan*, 87  
     intractable, chordotomy for, *Jan*, 98
- Paralysis, Erb's, *Jan*, 19
- Klumpke's, *Jan*, 19
- Patellar clonus in pyramidal tract lesions, *Jan*, 57
- Periarteritis nodosa, *Jan*, 139
- Peripheral nerve injuries, diagnosis and surgical treatment, *Jan*, 9
- Pernicious anemia, *Jan*, 229  
     clinical types, *Jan*, 230  
     liver therapy, *Jan*, 242  
     posterolateral sclerosis in, management, *Jan*, 245
- Peroneal nerve injuries, *Jan*, 20
- Potassium in myasthenia gravis, *Jan*, 135
- Pregnancy, macrocytic anemia of, *Jan*, 247
- Progesterone therapy in menstrual disorders, *Jan*, 263
- Prostigmine in myasthenia gravis, *Jan*, 131  
     diagnostic test, *Jan*, 128
- Protrusion of intervertebral disk, *Jan*, 111
- Psychiatrist, function of, in court, *Jan*, 211
- Psychoses, criminal responsibility in, *Jan*, 195  
     electroshock therapy, outpatient, *Jan*, 165  
     with insomnia, electroshock and insulin shock therapy *Jan*, 192
- Psychotherapy in insomnia, *Jan*, 186
- Pyramidal tract signs, pathologic, *Jan*, 45

- QUINIDINE in auricular fibrillation, *Jan.*, 217  
 in auricular flutter *Jan* 223  
 in paroxysmal tachycardia, *Jan* 226  
 uses and abuses, *Jan.*, 215  
 Quinine test for myasthenia gravis, *Jan.*, 129
- RADIAL nerve injuries, *Jan* 10  
 Radiculoneuritis, acute, infectious, *Jan.*, 1  
 Retrogasserian neurectomy classical, for facial pain *Jan* 80  
 posterior for facial pain *Jan.*, 83  
 Rossolimo sign in pyramidal tract lesions, *Jan* 53
- SCHIZOPHRENIA *Jan.*, 150  
 modern concept of *Jan*, 147  
 Sciatic nerve injuries, *Jan* 20  
 Sclerosis, posterolateral management in pernicious anemia *Jan.*, 245  
 Shock therapy of psychoses, *Jan.*, 165  
 Sleeplessness, *Jan*, 178  
 clinical effects, *Jan.*, 181  
 treatment, *Jan* 184  
 Spiller Frazer operation for facial pain *Jan.*, 80  
 Sterility hormone therapy *Jan* 258  
 261  
 Subdural hematoma *Jan* 62  
 Suprapatellar reflex in pyramidal tract lesions, *Jan* 57  
 Suture, primary in peripheral nerve injuries, *Jan* 25
- TACHYCARDIA, paroxysmal, quinidine in, *Jan* 226  
 Testosterone in menstrual disorders, *Jan.*, 265  
 Thiamine hydrochloride in facial pain *Jan.*, 77  
 Thymectomy for myasthenia gravis, *Jan.*, 136  
 Tibial nerve injuries, *Jan.*, 22  
 Tractotomy, medullary, for facial pain *Jan.*, 84  
 Transfusions, blood, in pernicious anemia, *Jan.*, 245  
 Trichlorethylene in facial pain, *Jan.*, 77  
 Trigeminal neuralgia, *Jan.*, 73  
 atypical *Jan* 85  
 symptomatic, *Jan.* 75  
 Trigger zones in trigeminal neuralgia, *Jan.*, 74  
 Trömmers technic for Hoffmann sign *Jan.*, 34  
 Tumors, facial pain due to *Jan* 91
- ULNAR nerve injuries, *Jan* 15  
 Ulnar median nerve injuries, *Jan.*, 18  
 Uterine bleeding functional, hormone therapy *Jan.*, 259, 261, 264, 266
- VERBANA, *Jan.*, 147  
 Vitamin therapy in pernicious anemia, *Jan.*, 244
- Wrist clonus in pyramidal tract lesions, *Jan.* 57



*This edition is produced in compliance with the Government's regulations for conserving paper and other essential materials*

## CONTENTS

### SYMPOSIUM ON NEW DEVELOPMENTS IN MEDICINE

FROM THE JOHNS HOPKINS UNIVERSITY SCHOOL OF MEDICINE AND  
THE JOHNS HOPKINS HOSPITAL, BALTIMORE, MARYLAND

	PAGE
The Modern Treatment of Cirrhosis of the Liver By Dr W Halsey Barker	273
The Use of Sulfamerazine in Pneumococcal Pneumonia By Drs. A Genecin and R A Nelson	294
Thiouracil and Hyperthyroidism By Dr Elliot V Newman	302
Medical Mycology By Dr Edmund L Keeney	323

FROM THE UNIVERSITY OF MINNESOTA MEDICAL SCHOOL AND  
THE UNIVERSITY OF MINNESOTA HOSPITALS,  
MINNEAPOLIS, MINNESOTA

The Diagnosis and Treatment of Brucellosis By Drs. Wesley W Spink and Wendell H Hall	343
Cirrhosis of the Liver With Particular Reference to Correlation of Composite Liver Function Studies with Liver Biopsy By Drs. Frederick W Hoffbauer, Gerald T Evans and Cecil J Watson	363
Hyperparathyroidism By Dr Edmund B Flink	389
The Restriction of Activity in Coronary Occlusion with Particular Reference to the Extent of Myocardial Infarction By Drs G N Aagaard and C. J Watson	405

# CONTENTS

## FROM THE TULANE UNIVERSITY SCHOOL OF MEDICINE AND THE OCHSNER CLINIC, NEW ORLEANS, LOUISIANA

Recent Advances in Pharmacology	PAGE 417
By Drs Edgar W. Warren and Thomas Findley	
Recent Advances in the Treatment of Tuberculosis	445
By Dr Julius L Wilson	
Some Recent Advances in Bronchial Asthma	453
By Dr Vincent J Derbes	
The Ventricular Gradient	464
By Dr George Burch	

## FROM THE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST LOUIS, MISSOURI

Recent Advances in the Therapy of Cirrhosis of the Liver	479
By Dr Leo J Wade	
Diagnosis of Gastroduodenal Disease	489
By Dr John L Horner	
Diagnosis and Treatment of Pleural Effusions	502
By Dr Alfred Goldman	
Differential Diagnosis of Precordial Pain	513
By Dr Julius Jensen	

## FROM THE STANFORD UNIVERSITY SCHOOL OF MEDICINE, SAN FRANCISCO, CALIFORNIA

The Clinical Use of Digitalis Preparations	524
By Dr J K Lewis	
Clinical Relationships between Arterial Hypertension and the Kidneys	535
By Dr David A Rytand	
Modern Methods Used in Finding Pulmonary Tuberculosis and Treatment of the Asymptomatic Case	544
By Dr Philip H Pierson	
Cumulative Index	555

# THE MEDICAL CLINICS of NORTH AMERICA

---

NATIONWIDE NUMBER

---

## SYMPOSIUM ON NEW DEVELOPMENTS IN MEDICINE

---

### THE MODERN TREATMENT OF CIRRHOSIS OF THE LIVER

W HALSEY BARKER, M.D.\*

Prior to the last decade the treatment of cirrhosis of the liver was largely symptomatic. A high carbohydrate diet was sometimes utilized on the grounds that carbohydrates exerted a sparing action upon the liver. Since alcohol was thought to be an important etiologic factor, the victim of cirrhosis was urged to become a total abstainer. Diuretics and paracentesis were employed as indicated for relief of ascites, and at times the surgeon was called upon to perform an omentopexy. However, none of these measures was of more than temporary value, and the prognosis in cirrhosis, once ascites had developed, continued to be practically hopeless. Indeed, it was in the rarest of cases that ascites ever cleared up. Ratnoff and Patek<sup>1</sup> present an excellent discussion of the natural history of Laennec's cirrhosis of the liver in their analysis of 386 cases.

#### ETIOLOGY OF CIRRHOSIS

The etiology of cirrhosis of the liver remains far from settled. In searching for factors that predispose to cirrhosis and thus may bear upon its etiology, Patek<sup>2</sup> found one glaringly prominent fact, namely, that *alcoholism* is the most common antecedent factor in this disease in the Western Hemisphere. Yet in about 30 per cent of cases seen at autopsy, there had been no story of alcoholism. Furthermore, when he examined the data on chronic alcoholism, he found that only a small proportion of the victims, variously estimated at from 1 to 25

---

From the Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.

\*Associate in Medicine, Johns Hopkins University School of Medicine, and Physician in-charge, Clinic for Gastro-Enterology and Nutritional Diseases, Johns Hopkins Hospital.



per cent, develop Laennec's cirrhosis. It seemed probable that the association was intimate but not direct, that alcoholism per se did not cause cirrhosis of the liver. The fact that the disease occurs commonly in India, Java and Ceylon, where alcoholism is rare, would support this interpretation. Moreover, there would seem to be incontrovertible evidence that cirrhosis may follow severe toxic hepatitis (e.g., from carbon tetrachloride or arsenical drugs) and so-called infective or epidemic hepatitis in nonalcoholic individuals.

Since alcoholic beriberi and pellagra had been shown to be similar to the endemic forms of these diseases, it seemed plausible to Patek that the correlation between alcoholism and cirrhosis of the liver might also be due to a coexisting *nutritional deficiency*. This hypothesis appeared particularly attractive in view of the high incidence of vitamin B-complex deficiency noted in patients with cirrhosis, as, for example, Wayburn and Guerard's<sup>3</sup> report of multiple peripheral neuropathy in 17 per cent of a large series of cirrhotic patients. The trouble with the severe alcoholic is that he forgets to eat, thus it seems fair to assume that many of the various morbid states to which an alcoholic is subject are primarily manifestations of vitamin deficiency. Although alcohol conceivably may exert toxic effects in the face of a poor diet, it must play a minor role at best, since all of the deficiency syndromes may develop in total abstainers on deficient diets.

An abundance of experimental evidence has accumulated attesting to the etiologic role of nutritional deficiency in the production of liver disease. In 1924, Allan and his associates<sup>4</sup> reported that depancreatized dogs receiving adequate amounts of insulin and a diet of lean meat, sucrose and bone ash did not survive for longer than a few months. They also observed that failure of liver function due to fat infiltration of the liver found in such animals could be prevented by adding raw pancreas to the diet. These observations provided the necessary stimulus for a tremendous amount of research on lipotropic substances,<sup>5</sup> or substances preventing fat deposition in the liver, among them lecithin, "lipocair," choline and inositol. MacLean and Best<sup>6</sup> in 1934 reported that fat was deposited in the liver of rats kept on a high-fat intake and this fatty deposition could be prevented by giving sufficient choline (now generally regarded as a member of the vitamin B complex). Subsequently, Gyorgy and Goldblatt<sup>7</sup> produced fatty livers with necrosis in rats maintained on a diet deficient in the vitamin B complex even though supplemented with thiamine, riboflavin and pyridoxine. The addition to the diet of yeast, a yeast extract, or 2 mg of choline a day usually prevented the changes in the liver. Rich and Hamilton<sup>8</sup> succeeded in reproducing true cirrhosis of the liver in rabbits fed a deficient diet. The development of this experimental cirrhosis was not prevented by the addition of thiamine, riboflavin, pyridoxine, nicotinic acid or vitamins A, D and E to the basal diet,

whereas a daily supplement of 5 gm. of dry brewer's yeast gave full protection Rhoads and Miller<sup>9</sup> observed that the ability of the liver to excrete intravenously injected bilirubin was reduced in dogs when the animals were fed a diet lacking in the vitamin B<sub>2</sub> complex and that this function could be restored by the feeding of a normal diet or by the administration of crude liver extract. Many other studies indicate a protective action against hepatotoxins by the feeding of yeast, choline, methionine or high protein diets.

Interpretation of disease in man in the light of experimental work in animals must be made with the utmost caution. However, certain clinical observations already mentioned suggest that *vitamin deficiency* may be an all-important etiologic factor in fatty liver and cirrhosis of the liver in human beings. Undoubtedly, clinical and experimental observations were of equal importance in giving impetus to the development of the modern treatment of cirrhosis by a nutritious diet high in calories, protein and vitamins. Before taking up the details of this dietary treatment of cirrhosis, it might be well to review briefly the symptomatology of the disease and the factors affecting the prognosis.

#### SYMPTOMATOLOGY AND PHYSICAL SIGNS

The most important symptoms of cirrhosis in Patek's large series were, in order of frequency, as follows: abdominal swelling, peripheral edema, weight loss, nausea and vomiting, abdominal pain, and hematemesis. The most common *initial* symptoms and signs occurred in the following order: swollen abdomen, abdominal pain, hematemesis, edema of legs, jaundice, nausea and vomiting and weakness. Physical signs in the series of 386 patients were listed thus: ascites 78 per cent, palpable liver 75 per cent, jaundice 65 per cent, edema 61 per cent, palpable spleen 44 per cent, hemorrhoids 27 per cent, fever 24 per cent, collateral venous circulation 23 per cent, vascular spiders 15 per cent, and a number of other less specific manifestations, among them hemorrhagic phenomena.

#### CLINICAL COURSE AND PROGNOSIS

Ratnoff and Patek succeeded in following 245 of their series of 386 patients until their death, more than 60 per cent of these deaths occurred within one year of the first symptoms of the disease. An additional 117 patients were lost to follow-up, leaving only twenty-four patients known to be alive at the time the records were reviewed. Spontaneous loss of ascites occurred in only about 7 per cent of the cases. After the onset of ascites 47 per cent of the patients survived six months, 32 per cent one year, and but 17 per cent survived two years. Following the onset of jaundice (superimposed upon pre-existing cirrhosis) the survivorship curve was very similar to that following the onset of ascites. Of the 106 patients in the series who

suffered from hematemesis, 40 per cent died within one month of the initial hematemesis, with an additional 30 per cent succumbing by the end of the first year. However, if a patient survived one year following hematemesis, he had a good chance of surviving several years longer.

The most common causes of death in cirrhosis, according to these same authors, are *liver failure* or *cholema*, an ill-defined state in which the patient may become stuporous or delirious, finally sinking into coma (jaundice is usually but not invariably present), *hematemesis* from ruptured esophageal or gastric varices, and *secondary infections*.

The prognosis following omentopexy, should the patient survive the initial postoperative period, was at first considered to be better than without treatment. Recent studies, however, indicate that although improvement may be noted in individual instances, the average prognosis for patients with cirrhosis is not appreciably changed by operative therapy. There were thirty-four postoperative deaths in Ratnoff and Patek's series, representing an operative mortality of 40 per cent.

#### DIETARY TREATMENT OF CIRRHOSIS

In 1937 Patek<sup>10</sup> published a preliminary report on the treatment of alcoholic cirrhosis with a nutritious diet together with vitamin supplements. Convinced that the improvement that followed treatment appeared to be outside chance expectations, he was encouraged to extend the program of treatment to embrace a larger series of patients over a longer period of time and he recognized the importance of comparing the course of patients so treated with that of a similar group of hospitalized patients who had not received special dietary therapy. This led to the review of the 386 "untreated" cases by Ratnoff and Patek,<sup>1</sup> the 1941 report by Patek and Post<sup>11</sup> on fifty-four patients with decompensated cirrhosis treated with the new dietary regimen, and the 1943 paper by Patek<sup>2</sup> furnishing a more recent follow-up on the 1941 series.

Through a careful analysis of the symptomatology and physical signs in his group of fifty-four "treated" patients and a comparison of the figures thereby obtained with those for the "untreated" group of 386 patients, Patek was able to present convincing evidence that the "treated" group prior to receiving treatment was, if anything, more severely afflicted than the "untreated" group. Eighty-nine per cent of the "treated" patients had ascites when first observed, while 63 per cent had jaundice and 24 per cent gave a history of hematemesis. In other words, it is fair to conclude that the "treated" and control series are entirely comparable as far as severity of the liver condition is concerned. And as a corollary to this conclusion, it would seem justifiable to accept any statistically supported improvement in the average survival period for the treated group as distinctly significant.

What then is this *Patek dietary regimen*? The diet is rich in protein and ample in carbohydrate and fat. Containing approximately 3600

calories, it is distributed in the following proportions protein 139 gm (including the protein in the brewer's yeast), fat 175 gm., and carbohydrate 365 gm. The diet\* consists largely of meat, milk, eggs, fruit and green vegetables. Meat is served twice daily, milk five times daily—three times with meals and twice with 25 gm of powdered brewer's yeast. The yeast is fed in graded, increasing doses up to the final amount. Even so, certain patients cannot tolerate brewer's yeast, for these, oral vitamin B complex has been substituted in the form of liquid yeast concentrates. In addition, thiamine hydrochloride (5 mg) is injected intramuscularly every day, and concentrated liver extract (5 cc) twice weekly. During the critical period of hepatic decompensation the cirrhotic patient, to whom food is often loathsome, presents a real challenge to nursing and dietetic care. Patek urges that the intake at each meal be charted in order to keep account of the actual consumption. In patients with ascites salt intake is restricted only by the exclusion of a salt shaker from the tray, fluids are allowed up to 2000 cc. daily. Too rigid restriction of salt and water may prove harmful to these patients by precipitating symptoms of hypochloremia and dehydration. It should be pointed out that, with each abdominal tap, considerable salt is removed as well as an appreciable quantity of protein. Nonetheless, it is desirable to tap abdominal fluid before the patient is too distended, for this interferes seriously with the appetite. In an attempt to space out the intervals between paracenteses, mercurial diuretics may be injected once or twice a week following the oral administration of 3 to 4 gm of ammonium chloride daily for several days.

Of Patek's fifty-four patients treated on this regimen, twenty-two showed signs of progressive failure and went on to die, eighteen of them succumbing within the first five months of starting treatment. Twelve of the fifty-four patients were partially improved as shown by the loss of ascites and improvement in liver function tests, five were lost sight of, three remained free of ascites but failed to regain robust health, while four subsequently died after being ascites-free for over two years in each instance. The remaining twenty of the fifty-four patients were regarded as showing signs of "clinical recovery," their improvement fulfilling three criteria: (1) gain in weight and strength permitting the patient to resume his previous activity, (2) loss of ascites, edema and jaundice without recurrence, (3) changes in serum proteins, Takata-Ara and bromsulfalein excretion tests *towards* normal values. In the latter group although it seemed highly unlikely that the histologic changes were completely reversed it was clear that the process had been arrested or partially reversed.

Comparing the control and "treated" series Patek and his associates showed that 60 per cent of the treated patients, in contrast to only about 7 per cent of the control group, experienced the spontaneous

Complete dietary list may be found in the article by Patek and Post.<sup>11</sup>

disappearance of ascites The period of survival of patients after the onset of ascites showed the following differences

	Control	Treated
At 6 months	57%	72%
At 1 year	37%	57%
At 2 years	22%	45%

These figures have been subjected to statistical analysis and their significance has been established beyond the shadow of a doubt Patek predicts that far superior results might be expected if the dietary treatment could be instituted earlier in the disease before signs of hepatic decompensation had appeared

His interest stimulated by Patek's original report on the dietary treatment of cirrhosis and the volume of suggestive experimental work already mentioned, Snell<sup>12</sup> began treating cirrhotic patients with a nutritious diet supplemented with various vitamins His regimen differed materially from that recommended by Patek The diet was high in carbohydrate (500 gm), low in fat (about 60 gm), and rich in proteins not derived from meat sources (110 gm), providing roughly 3000 calories per day The protein component of the diet was derived chiefly from vegetables, milk and egg-white, meat being kept at a minimum The basis for this change in protein composition was Bollman's report that animals with experimentally produced hepatic injury are made worse by the administration of meat or meat extracts while tolerating protein from other sources without harmful effect Snell supplemented his diet with various pure vitamins, crude oral liver extract, and yeast or yeast concentrates In order to facilitate absorption of fat-soluble vitamins, patients were given animal bile salts, 0.3 to 1.0 gm with each meal This program gave very encouraging results in a group of fifty decompensated cirrhotic patients so treated A few remarkable "cures" with disappearance of ascites were encountered, one of the most striking in a man aged 72 who after two years of almost weekly paracentesis remained free of ascites and in good health for one year The results of treatment were regarded as "excellent" in 44 per cent of the entire group,<sup>13</sup> although only 22 per cent were entirely free from ascites at the time of the report Snell agrees with Patek that an even higher incidence of "cures" is to be expected among patients who present various degrees of fatty metamorphosis, degeneration and necrosis without extensive periportal fibrosis and great restriction of portal blood flow

In a recent report on the diagnosis and clinical course of fatty liver in seventy alcoholic patients, Keefer and Fries<sup>14</sup> stress the therapeutic value of a high-carbohydrate, low-fat diet with a moderate amount of protein, supplemented with vitamin preparations and liver extract. They regard the fatty liver as the precursor of cirrhosis, but point out that ascites, jaundice, and death may occur during the stage when the

liver is filled with fat and before actual fibrosis has developed. In some cases, the process appeared to be reversible. The recognition of this disorder in its early stages and the use of appropriate treatment was followed in many instances by recovery.

For the past several years we have been keenly interested in the dietary treatment of cirrhosis at the Johns Hopkins Hospital. To date too few patients have been so treated to justify any final conclusions, but we have seen sufficiently encouraging results to warrant a continuation of the regimen. In general, it has been our policy to adhere fairly closely to the Patek diet with the exception that the fat content of the diet has been considerably reduced for patients with jaundice or diarrhea. Since Snell's reasons for withholding meat are based on purely experimental grounds not necessarily applicable to the human liver and since meat is known to contain protein of "highest biologic value," we have not eliminated meat from our diet, but rather supplied it in liberal portions with complete impunity as far as we could ascertain. We have supplemented the diet with 30 to 50 gm of brewer's yeast powder a day and polyvitamin capsules in numbers sufficient to supply at least twice the estimated normal adult requirement for the vitamins of proven importance in human nutrition, namely vitamins A, C, D, thiamine, nicotinic acid (or the amide), and riboflavin. Where hemorrhagic phenomena were observed with prolongation of the prothrombin time, vitamin K was administered either parenterally or orally along with bile salts to promote its absorption. Intramuscular injections of crude (rather than concentrated) liver extract have been given in some cases, especially when macrocytic anemia was present. Furthermore, the oral administration of crude liver extract powder has been employed in certain instances. In view of the experimental work on the lipotropic action and protective effects exerted by choline on the liver, it seemed plausible to Wintrobe and the writer to administer this substance to patients with cirrhosis as an additional supplement to the measures already outlined. At least ten patients have now received choline chloride, 15 gm a day, administered in the form of a 10 per cent elixir prepared by the hospital pharmacy, in doses of 5 cc after each meal. No untoward effects have been noted after the continued administration of choline for weeks or even months. It is as yet too early to speculate upon the possible merits of choline therapy in cirrhosis.

#### ADJUNCTIVE THERAPEUTIC MEASURES

**Combating Secondary Vitamin Deficiency**—In addition to the highly suggestive evidence already presented that vitamin deficiency plays an important role in the etiology of liver disease, it has been firmly established that preexisting liver disease predisposes toward the development of numerous and varied manifestations of vitamin deficiency. Liver disease may contribute to the deficiency of the fat-soluble vitamins

A and K in one of three ways (1) failure of proper absorption in patients with jaundice, (2) failure of storage of the vitamins in the diseased liver, (3) disturbance of intermediary metabolism of the vitamins in the damaged liver. In patients with obstructive jaundice or hepatitis the dearth of bile salts in the intestinal tract results in poor absorption of fats and fat-soluble vitamins. Carotene furnishes the chief source of vitamin A in the average diet, and the normal liver converts carotene to vitamin A through the action of an enzyme, carotenase. Since a severely damaged liver will not effect this conversion, it is not surprising that low blood levels of vitamin A along with clinical manifestations of vitamin A deficiency (e.g., night blindness, keratomalacia, and epithelial metaplasia of various organs) have repeatedly been described in patients with cirrhosis or other forms of liver disease. Therapy or prophylaxis should consist in large doses of vitamin A administered orally with bile salts or large parenteral injections of vitamin A. Little improvement is to be expected from a high carotene intake in patients with severe liver damage.

The recognition of the etiologic role of vitamin K deficiency in the hemorrhagic diathesis so common in patients with jaundice or severe liver damage represents one of the most important contributions to medical knowledge within the last decade. This hemorrhagic tendency has been conclusively shown to be due to lowered plasma prothrombin, which in turn results from inadequate absorption of vitamin K, failure of the severely damaged liver to utilize vitamin K in the formation of prothrombin, or a combination of these two conditions. The failure of jaundiced patients to absorb vitamin K may be controlled by the oral administration of the bile salts along with vitamin K preparations or the parenteral administration of a purified vitamin K derivative such as 2-methyl-1, 4-naphthoquinone (1 to 4 mg. a day intramuscularly). If the liver is so severely damaged that it cannot produce prothrombin in spite of an adequate supply of vitamin K, bleeding will not be influenced by either of these methods of administering vitamin K and the prognosis becomes extremely grave. Under such circumstances, transfusions of freshly drawn blood should be given to supply prothrombin directly. The full understanding and proper application of these principles by surgeons and internists alike will go far toward decreasing risk from hemorrhage in jaundiced patients.

In addition to the special function of the liver with reference to vitamin A and K, the liver is known to serve as a storage depot for the majority of vitamins (A, B-complex, C, D, K) and probably provitamins as well. Hence, patients with severe liver disease are bound to have inadequate reserves and are, therefore, more likely to develop outspoken manifestations of vitamin deficiency under the added strain of any severe infection or curtailment of food. This situation affords still another reason for our advocating the liberal use of pure vitamins.

in addition to the high-vitamin diet and crude vitamin sources in the treatment of cirrhosis

**Treatment of the Anemia**—Macrocytic anemia with leukopenia is not an uncommon finding in patients with cirrhosis, even though their gastric juice may contain free hydrochloric acid and Castle's intrinsic factor. It has been postulated that this macrocytic anemia is due either to failure of the diseased liver to store adequate reserves of the anti-pernicious anemia principle or to improper metabolism of this principle in the diseased liver. This macrocytic anemia will respond to oral or parenteral therapy with liver extract in certain instances, but the response is rarely so dramatic or so complete as in patients with true pernicious anemia, and the macrocytic anemia of certain cirrhotics appears to be unaffected by liver therapy.

If there has been repeated blood loss from esophageal varices or constant oozing from hemorrhoids, the anemia in cirrhosis may be hypochromic and microcytic. In such cases iron therapy is indicated and best administered in the form of ferrous sulfate 0.2 to 0.4 gm. after each meal. Transfusions, of course, become necessary in patients suffering large or prolonged hemorrhages from ruptured varices.

**Diuretics and Paracentesis.**—When ascites or edema is present, the daily fluid intake should be limited to 2000 cc. and the salt intake moderately restricted to the extent of permitting no salt on the tray. Furthermore, since tense ascites interferes seriously with appetite, intestinal motility and the absorption of food, it is most important to combat this condition vigorously. It is desirable to postpone paracentesis as long as possible, hence, diuretic measures should first be given a trial. As a rule we give ammonium chloride (in the form of enteric-coated tablets) 3 to 4 gm. a day by mouth for several days, followed by one or more intravenous injections of mercupurin, 1 to 2 cc. at a time for one day to three days in a row. This procedure may be safely repeated at seven to ten day intervals. When diuretic measures fail to accomplish adequate relief from ascites, then paracentesis becomes imperative. The intervals between paracentesis can best be gauged by the weight curve, the condition of the abdomen, and the subjective status of the patient. There is no point in encouraging stoicism on this score.

**Surgical Treatment of Ascites and Varices.**—For many years the Talma operation or *omentopexy* (an operation designed to bring the omentum out into the abdominal wall in the hope of facilitating the development of collateral venous circulation) was thought to be a valuable measure for the relief of ascites. However, the operative mortality was high since cirrhotics tolerate anesthesia and surgical procedures poorly and the end results in those who survived were rarely good enough to arouse enthusiasm for this form of therapy. In recent years omentopexy has been largely discarded as a relatively useless therapeutic measure.

More recently *injection of a sclerosing agent* into esophageal varices



through an esophagoscope has been tried in an attempt to thrombose these veins and thereby prevent future hemorrhages. This procedure is a relatively new one and must await the test of time in a larger series of cases before its true value can be assessed. *Ligation of the coronary vein* of the stomach has been carried out in the hope of taking part of the load off of the esophageal varices. *Operative anastomosis of the splenic vein to the renal vein* has also been suggested as a means of shunting a considerable volume of blood away from the portal system, this is, of course, a modified Eck fistula.

The most radical surgical procedure designed to relieve ascites and to decrease the strain upon esophageal varices is *splenectomy*. From the hypothetical standpoint it would be desirable to remove the spleen in all cirrhotic patients with ascites or varices in order to reduce by no inconsiderable quantity the amount of blood entering the portal system. Unfortunately, the majority of patients with cirrhosis tolerate poorly prolonged anesthesia and the shock of such a major operative procedure. However, in selected cases splenectomy may be followed by striking improvement as illustrated in one of the cases to be reported briefly.

#### CASE REPORTS

In order to illustrate some of the therapeutic principles that have been described, we should like to present brief abstracts of four case records of patients treated by the writer within the last three years.

CASE I—J H., a white liquor salesman, aged 34, was first seen in February 1942 complaining of jaundice and abdominal swelling. His father, a heavy drinker, had died of cirrhosis of the liver in his 40's. Although always a nervous, high-strung person, the patient had enjoyed excellent health up until the winter of 1939 when he suffered a severe nervous shock as the aftermath of seeing his son struck by a truck. He lost his appetite, ate little, and slept poorly for the next eighteen months. During this period he took fruit juices, fruit, milk, bread and butter, but no vegetables, meat or eggs. He drank from 4 ounces to a pint of whiskey a day. He lost 30 pounds in weight and became so weak he was obliged to go to bed whence he was admitted to a hospital delirious with generalized edema and albuminuria. He was eventually discharged with a diagnosis of liver and kidney trouble. He returned to work very weak, but was eating better, including meat in his diet twice a week and three polyvitamin tablets daily. He claimed he took no more alcohol except two to five bottles of beer a day. In August 1941 he began to feel sluggish, lost his appetite, ate poorly once more, chiefly liquids, and again lost weight. In December, jaundice set in and progressively deepened with frequent light pasty stools and dark urine. There had been fluctuating swelling of the abdomen and legs during the six months prior to admission. There was no gross hemorrhage from the gastrointestinal tract, but some blood-streaking on the stools from straining.

The principal *physical findings* were deep jaundice, edema of the legs, numerous "spider" angiomas over the neck and shoulders, dental caries, lungs clear, heart pushed upwards and outwards, sounds clear except for systolic murmur at the apex, pulse regular, blood pressure 145/85, well marked ascites with evidence of collateral venous circulation over both flanks, liver tremendous with upper border of dullness at right fifth rib and lower edge felt 2 cm. below level of umbilicus on the right. The edge extended across the epigastrium just above

TABLE 1—LABORATORY FINDINGS IN CASE 1

Date	Serum Bilirubin (mg per 100 cc.)	Total Serum Protein (gm. per 100 cc.)	Serum Albumin (gm. per 100 cc.)	N.P.N. (mg per 100 cc.)	Serum Chloride (Meq. per L.)	CO <sub>2</sub> Comb Power (vols per 100 cc.)	W B C	Hgb in gm.	Vol. Packed R.B.C	Pro- thrombin Time in Seconds
March 2	16.5	4.76	2.56	40	92.4	53.2	17,200	14.5	42.2	62/20*
March 10	18.5			80	90.4	40.9	21,500	15.2	44.0	18/15
March 17	19.0	4.65	2.51	70	96.6	36.2	28,750	14.8	42.0	
March 23	14.0			60	101.6	33.4				
March 30	4.9				105.6	33.4	16,500	12.0	36.5	20/14
April 4	3.3	4.50		30	102.6	32.4†				
April 10	1.6	5.10		30	105.6	37.2	13,000	13.3	38.9	20/16
April 14	2.0			28	103.2	43.8	13,150	13.5		
April 24	1.2			30	102.8	51.3				
May 1	1.6	5.08	2.84	32	113.6	54.1				
May 12	0.6	4.75	2.73	25			4,800	16.0	48.8	19/19

\* Results of prothrombin time expressed as 62/20 means for patient 62 seconds as compared with normal control 20 seconds.

† At this time the serum sodium was distinctly low, 129.0 milliequivalents per liter.

the umbilicus to disappear beneath the left costal margin. The liver felt hard but smooth except for a notch between the lobes in the epigastrium. The spleen was not felt. There were no external hemorrhoids. Neurologic examination was normal.

The admission diagnosis was cirrhosis of the liver with a superimposed episode of acute hepatitis or hepatic necrosis. Neoplasm of the liver was considered possible but unlikely.

**Laboratory Findings** The blood count on admission showed no anemia but a marked polymorphonuclear leukocytosis: red blood cells 4,870,000, hemoglobin 14.5 gm or 100 per cent, volume packed red blood cells 42.2, giving normal indices, leukocytes 17,200 with juveniles 11 per cent, segmented neutrophils 81

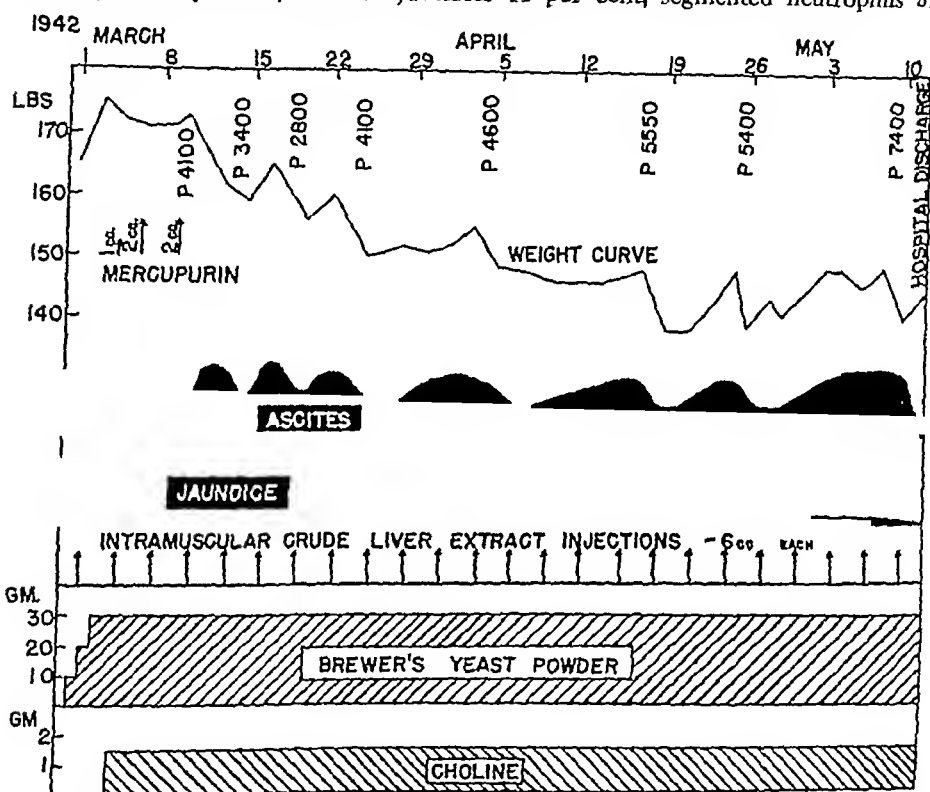


Fig 45 (Case I, J H) —Chart shows weight curve, fluctuating ascites, disappearance of jaundice, and various therapeutic measures employed over the 11-week period of hospitalization "P" equals paracentesis, the volume of ascitic fluid in cubic centimeters removed is designated for each paracentesis

per cent, lymphocytes 5 per cent, monocytes 3 per cent, sedimentation rate (Wintrobe method) markedly accelerated, 44 mm corrected to 36 mm. Urine was slightly cloudy, dark brown, specific gravity 1.010, acid, albumin 2 plus, bile 4 plus, urobilinogen negative, microscopic examination showed bile-stained hyaline and granular casts, but no erythrocytes, leukocytes or amino acid crystals. Serologic test for syphilis was negative. Stool was pasty gray, negative for occult blood and bile pigment. The remainder of the laboratory findings during the patient's stay in the hospital are summarized in Table 1.

**Clinical Course** Certain of the more important clinical features and therapeutic measures employed are depicted graphically in Figure 45. This patient was desperately ill on admission and seemed to grow worse during the first two

weeks with increasing jaundice, ascites which recurred rapidly after each paracentesis and failed to respond to diuretic measures, and an intractable fatty diarrhea which persisted for seven weeks, unaffected by orally administered bile salts or pancreatic enzymes. A diet high in protein, carbohydrate and vitamins but low in fat was prescribed, supplemented with brewer's yeast power 30 gm a day polyvitamin capsules\* (two a day), choline chloride 1.5 gm a day and intramuscular injections of 6 cc. crude liver extract every third day. Since the patient was too ill to consume his full diet, additional carbohydrate was supplied in the form of 10 per cent glucose intravenously almost every day for the first four weeks. He ran an irregular fever as high as 102° F at times. As a result of too rigid salt restriction and loss of sodium chloride at paracentesis, he became dehydrated with hypochloremia, prerenal azotemia and moderate acidosis. When the salt intake was increased the nonprotein nitrogen fell to normal as the blood chloride rose to a normal level. However, at this stage the acidosis was still pronounced as shown by the persistent reduction in the carbon dioxide combining power. Dr. George Thorn interpreted this acidosis as resulting from bicarbonate loss in which the prerenal azotemia and the strongly acid ash (high protein) diet were the chief contributory factors. The low serum sodium at a time when the serum chloride had returned to normal fits in with Dr. Thorn's interpretation. The patient became delirious and was extremely difficult to manage during the azotemic acidotic phase of his illness. The marked leukocytosis was thought to be due to extensive hepatic necrosis. In view of the much prolonged prothrombin time on admission, the patient was given synthetic vitamin K 2 mg intramuscularly daily for the first three weeks, 1 mg every second day thereafter. The fact that the prothrombin time improved under vitamin K therapy was one of the few encouraging signs during the early weeks of treatment.

Throughout the first three weeks little hope was held out for the patient's recovery. Then he rather suddenly began to improve as shown by increase in appetite, cessation of loss of flesh weight, return of mental faculties, diminution in size of the liver, decrease in jaundice with eventual return of serum bilirubin to normal, and gradual decline of white blood cells to normal. He was discharged from the hospital on May 12, ten weeks after admission on the full dietary regimen, and required no further paracentesis although it was necessary to administer intravenous mercupurin on May 22 and June 1 to combat recurrent ascites. He experienced an excellent diuresis on each occasion, and thereafter the ascites slowly subsided spontaneously.

When the patient was last seen on June 18 there was practically no ascites, the liver was only 3 cm. below the right costal margin, and the tip of the spleen was felt for the first time. He was feeling fine and had regained flesh. Shortly thereafter he returned to work. Repeated efforts to persuade the patient to report at regular intervals were unsuccessful. It was learned from his wife that after remaining abstemious and following his therapeutic regimen for several months, during which period he seemed perfectly well, he began drinking once more, stopped eating and eventually died in August 1943 with jaundice and ascites.

**Comment**—A 34 year old alcoholic liquor salesman was admitted to the hospital desperately ill with what was regarded as acute hepatic necrosis, presumably superimposed on underlying cirrhosis. His illness was characterized by fever, leukocytosis, deep jaundice, ascites

\* The polyvitamin capsule used in treatment of this patient and the other three patients was Dayamin (Abbott). Each capsule contained vitamin A, 10,000 U.S.P. units; vitamin D, 1000 U.S.P. units; thiamine hydrochloride, 3 mg; riboflavin, 2 mg; ascorbic acid, 50 mg; nicotinamide, 20 mg.; pyridoxine hydrochloride, 1 mg; pantothenic acid, 1 mg.

and fatty diarrhea. On a modified Patek regimen, including the oral administration of choline chloride and intramuscular crude liver extract, he made a remarkable recovery with complete clearing of jaundice and ascites, only to succumb fifteen months later after returning to his alcoholic ways and abandoning his therapeutic regimen. This type of patient should have excellent prospects of a permanent "cure" provided he could be maintained indefinitely on a nonalcoholic regimen with a nutritious diet.

**CASE II—P. B.**, a white retired businessman and farmer, aged 66 years, was admitted to the hospital on March 10, 1944 complaining of jaundice, abdominal swelling and loss of appetite. His father had died of cancer of the throat. The patient had enjoyed excellent general health throughout his life up to the onset of the present illness. For ten years he had noted a postnasal drip and nasal obstruction, attributed to sinusitis. He had also suffered from arthritis of his shoulders and back for at least ten years. For many years he had been a heavy drinker with the exception of one period of seven to eight years when he stopped drinking entirely. Throughout the ten years prior to the onset of the present illness he had consumed at least 1 quart of distilled spirits a week. He claimed to have eaten fairly well over this period. During the summer of 1943 the patient began to suffer from postprandial epigastric pain, he lost his appetite and was afraid to eat, although he remained partial to small servings of rare red meat. His total daily food intake was very poor and he lost a great deal of weight. Six weeks before admission he developed jaundice with generalized pruritus. This was followed by marked swelling of the abdomen and legs. There had been no hemorrhagic phenomena.

On *physical examination* the patient was an unusually tall, large framed man who seemed somewhat confused mentally. He showed evidence of weight loss over the upper half of the body, with pronounced soft pitting edema over the legs, abdomen and lower back. The complexion was bronzed with slight icterus, no vascular "spiders" were seen. The tongue was normal, lungs were clear with definite emphysema, the heart was not enlarged, sounds distant with a soft systolic blow all over, pulse regular, moderate arteriosclerosis, blood pressure 155/80. The abdomen was hugely distended with bulging in the epigastrium and both flanks, marked shifting dullness and suggestive fluid wave. The liver and spleen were not felt, there were no hemorrhoids. The neurologic examination was negative except for absent ankle jerks and questionably diminished vibratory sense in the legs.

The *admission diagnosis* was cirrhosis of the liver with ascites and mild jaundice, probably on a dietary deficiency basis in a man with a background of over-indulgence in alcohol. Carcinoma of the tail of the pancreas was considered possible but less likely.

*Laboratory Findings* Blood count: red blood cells 4,320,000, hemoglobin 13.8 gm or 95 per cent, volume packed red blood cells 39.6 giving normal indices (the blood remained normocytic and normochromic throughout), leukocytes 8300 with polymorphonuclear neutrophils 81 per cent, polymorphonuclear eosinophils 1 per cent, lymphocytes 8 per cent, and monocytes 10 per cent, sedimentation rate 50 mm corrected to 36 mm in one hour (Wintrobe method). Urine was orange, clear, acid, specific gravity 1.016, no sugar or albumin, faintly positive for bile, strongly positive for urobilinogen up to 1:320 dilution, occasional leukocytes, hyaline and granular casts. Serologic test for syphilis was negative. The prothrombin time was 17 seconds as compared with normal control of 16 seconds. The remainder of the more important laboratory results throughout the period of observation are summarized in Table 2.

TABLE 2—LABORATORY FINDINGS IN CASE II

Date	Serum Bilirubin (mg per 100 cc.)	Total Serum Protein (gm. per 100 cc.)	Serum Albumin (gm. per 100 cc.)	N P N (mg per 100 cc.)	Serum Chloride (Meq per L.)	W B C	Hgb in gm.	Vol. Packed R.B.C	Brom sulfalein Retention After 30 Minutes	Hippuric Acid Excretion in gm *
March 11	2.7	6.75	2.31	25	104.8	8300	13.8	39.6	25%	0.28
March 14										
March 15	0.8	7.81	2.19	25		7200	13.7	37.7		
April 25	0.9	6.63	2.00	31		7950	13.0	36.5		
April 25	0.8	6.13	2.13	23	101.0	4150	12.3	34.0	7%	
May 16	0.8	7.31	3.00	29	95.0	6300	12.6	38.2		
June 28	0.9	6.13	3.19	34	107.0	5000	11.9	34.7	7%	1.15
Sept. 20										

\* Normal result is 1 gm. or more excreted within one hour after intravenous injection of 1.77 gm. of sodium benzoate

*Clinical Course* Important features in the clinical course and therapy of this patient are charted in Figure 46. He was kept upon the full Patek diet from the start. This was supplemented daily with 30 gm of brewer's yeast powder, three polyvitamin tablets, and later 15 gm of choline chloride. In addition he was given an intramuscular injection of 2 cc of parentosol-B\* daily for the first seven weeks. Two intramuscular injections of crude liver extract caused so much local discomfort that this form of therapy was abandoned. The chart demonstrates the striking diuresis obtained on each occasion from combined therapy with oral ammonium chloride (enteric-coated tablets) and intravenous mercu-

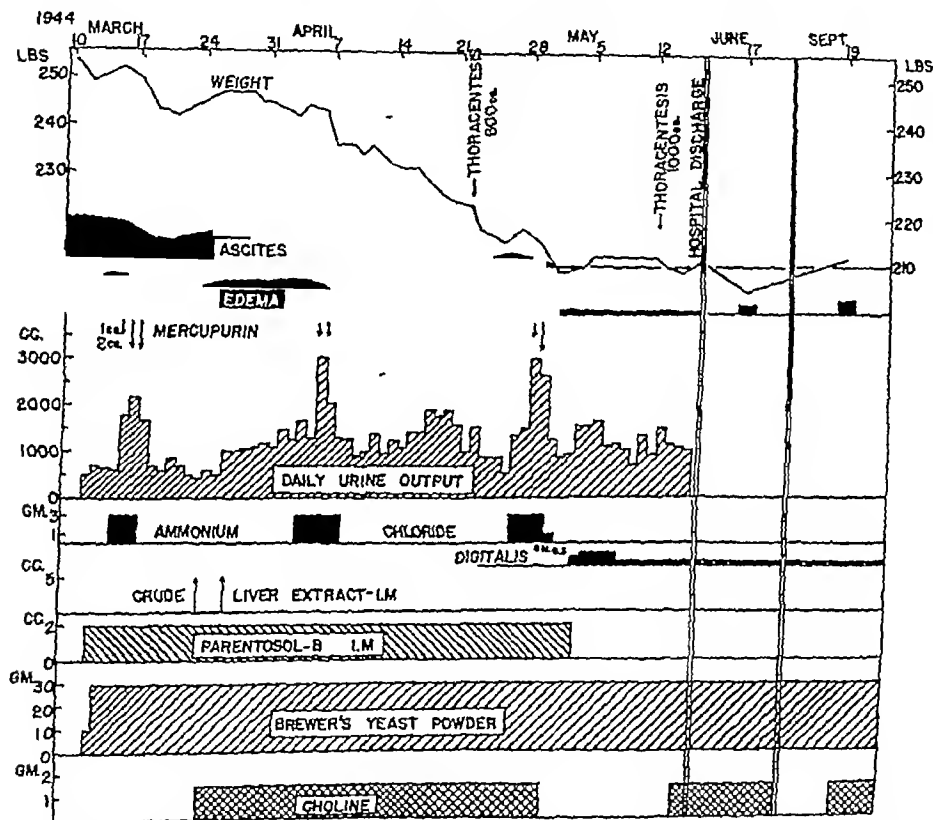


Fig 46 (Case II, P B) —Chart shows progressive loss of weight (due largely to clearing of ascites and edema), the daily urine output (with striking diuresis on each occasion that oral administration of ammonium chloride was followed by intravenous mercupurin), and various therapeutic measures employed over the 10-week period of hospitalization in March, April and May, also status of patient at subsequent periods of observation in June and September

purin, also the increasing tendency to spontaneous diuresis after the patient had been under treatment for several weeks. Since the fluid intake was kept fairly constant throughout (never over 2000 cc in one day), the fluctuation in urinary output may be regarded as significant. The loss of 40 pounds in weight shown on the chart may be attributed almost entirely to steady decrease in edema and ascites, as there was little evidence of actual loss of flesh. The ascites had dis-

\* Parentosol-B (Squibb) is provided in sterile ampules for parenteral use. Each cubic centimeter contains thiamine hydrochloride 10 mg., riboflavin 4 mg., and niacinamide 200 mg.

appeared completely after seven weeks, at which time the hard liver was readily palpable 4 cm below the right costal margin and the tip of the spleen could also be felt.

After four weeks on the therapeutic regimen the patient began to exhibit evidence of steady improvement as shown by the diminishing ascites and edema the disappearance of the slight icterus with return of the serum bilirubin to normal and the decrease in bromsulfalein retention. The serum albumin remained low around 2.0 gm. per 100 cc. throughout his hospital stay. This hypalbuminemia was thought to be an important contributory factor in the edema, ascites and the right hydrothorax which developed six weeks after admission. The only peculiar features of the hydrothorax were (1) that it appeared at a time when the edema and ascites had almost cleared up and (2) that the chest fluid had an unusually high protein content (3.88 gm. per 100 cc.) and cell count (7650) for a transudate. An underlying pulmonary infarct and cardiac failure on an arteriosclerotic basis were considered as possible alternative explanations for the hydrothorax. In view of a potential element of cardiac failure, the patient was digitalized without obvious effect on the hydrothorax or the urinary output.

The patient was discharged from the hospital on May 17 in excellent condition. He was reexamined in June and September. There was no recurrence of ascites or jaundice on either occasion. Moderate edema of the legs had been present ever since he became ambulatory once more. The steady rise in serum albumin to 3.19 gm. per 100 cc. on September 20 along with the normal hippuric acid excretion test on the same date furnished convincing objective evidence of improvement in his liver function. Latest reports from the patient in November 1944 eight months after dietary treatment was inaugurated, attest to his continued good health. He has adhered strictly to the Patek diet with yeast and vitamin supplements, while taking courses of choline intermittently, ever since discharge from the hospital.

*Comment*—This 66 year old man with cirrhosis of the liver, quite conceivably on a dietary deficiency basis, made an excellent response to the Patek regimen supplemented with choline chloride. Since there was an excellent response to diuretic measures on three separate occasions, paracentesis was at no time necessary. The patient has remained free of jaundice and ascites for over six months, while a steady rise in serum albumin, decrease in bromsulfalein retention, and increase in hippuric acid excretion (following the injection of sodium benzoate) furnish additional objective evidence of improvement in liver function.

**CASE III**—E. H., a white male restaurant owner and bartender aged 56 years, was admitted to the hospital on March 3, 1943 complaining of abdominal swelling of three months duration. Family history was noncontributory. Past history revealed nothing of unusual interest except for the fact that the patient had been a heavy drinker of both beer and distilled spirits for many years. For six months prior to admission he had been eating very poorly as he put it he was "too busy to eat." He would eat chiefly potatoes and butter rarely meat, fruit or vegetables. During the six months he lost 30 pounds in weight. In December 1942, there was insidious onset of painless abdominal swelling which gradually increased. He had not noticed jaundice and had never suffered a gastrointestinal hemorrhage. There had been some swelling of the legs for several months.

The principal findings on physical examination were as follows: evidence of marked weight loss with striae on arms; slight icterus; soft pitting edema over legs and lower back with stasis eczema on lower legs; red papular eruption over



face and numerous vascular "spiders" over neck, arms and upper trunk, beefy red smooth geographical tongue, chest emphysematous, lungs clear, heart normal in size with regular rhythm and blood pressure 140/70, abdomen hugely distended with ascites, collateral venous circulation over abdominal wall. No organs or masses were felt prior to tapping the abdomen. Following paracentesis the abdomen was soft, the hard, somewhat irregular liver edge was felt just below the right costal margin and extending across epigastrium 5 cm below xiphoid. Spleen was not felt. Neurologic examination was entirely normal.

The *admission diagnosis* was cirrhosis of the liver with jaundice and ascites, probably on a dietary deficiency basis in a heavy alcoholic.

*Important Laboratory Findings* Blood count red blood cells 4,280,000, hemoglobin 13.8 gm or 95 per cent, volume packed red blood cells 39.9 giving mean corpuscular volume of 93 cu microns (a figure slightly on the macrocytic side), leukocytes 7850 with normal differential count, sedimentation rate markedly elevated to 51 mm (corrected to 37 mm.) in one hour, icterus index 18. Urine showed 1 to 2 plus albumin, urobilin but no bilirubin. Serologic test for syphilis was negative. The blood nonprotein nitrogen was 30 mg per 100 cc, fasting sugar 85 mg per 100 cc., chloride 102.6 milliequivalents per liter, total serum protein 7.50 gm per 100 cc with albumin 3.06 gm and globulin 4.44 gm per 100 cc, van den Bergh test gave a delayed biphasic reaction with serum bilirubin 1.8 mg per 100 cc. Liver function tests. Bromsulfalein test showed 30 per cent retention after thirty minutes, hippuric acid test revealed only 0.11 gm excreted at the end of one hour. Prothrombin time 24 seconds compared with normal control of 13½ seconds. Stool showed bile and gave a faintly positive test for occult blood.

*Course.* The patient was placed on the Patek diet (except that fat content was reduced), supplemented with brewer's yeast 45 gm, 10 per cent elixir choline 15 cc., one polyvitamin capsule, and 3 mg of vitamin K daily by mouth. Paracentesis was performed the day after admission, yielding 10,500 cc of straw-colored fluid with specific gravity 1.016, protein 10 gm per liter, 300 cells (chiefly lymphocytes). The patient remained in the hospital for eight weeks during which time he lost ground steadily, his weight falling from 175 to 137 pounds. He experienced great difficulty in taking his full diet although he made a sincere effort. Paracentesis was performed six times in all, yielding 8000 to 13,000 cc. of fluid at each tap. Ascites reaccumulated rapidly after each tap in spite of restricted intake of fluid and salt. Attempts to relieve the ascites with ammonium chloride and mercupurin met with only slight success, insufficient to forestall the necessity for repeated paracenteses. The prothrombin time failed to improve materially following the administration of vitamin K either orally or intramuscularly (this observation is of ominous import as regards the severity of the liver damage). The bromsulfalein retention was 25 per cent at the end of the hospital stay, a value almost identical with the original figure.

After discharge from the hospital the patient attempted to follow the entire regimen at home, but continued to lose weight. He required taps at weekly intervals, eventually became wildly delirious and died on July 14 following a massive hematemesis.

*Comment*—This case represents an instance of cirrhosis so advanced that the pathologic changes must have been completely irreversible. In spite of the dietary regimen instituted, the course was progressively downhill to death. One point of special interest was the failure of the prothrombin time to return to normal after adequate parenteral therapy with vitamin K, an indication of the severity of the parenchymal liver damage.

CASE IV—E. K., a white male electrician, aged 39 years was admitted to the hospital March 26, 1943 complaining of abdominal swelling for nearly two years. The family history was noncontributory. In the past history it was of interest that up to 1936 he had worked in a rubber heel business where he was exposed to fumes of sulfur and various solvents. There was no exposure to chemicals thereafter. Early in 1940 he suffered a severe electric shock which knocked him unconscious and caused serious burns. He spent six weeks in a hospital at the time. Appetite had been excellent with well balanced diet, and alcohol had been taken sparingly at best, not over four glasses of beer a month. In August 1941 he noticed increasing weakness, malaise and fatigue. One month later he suffered massive hematemesis two days apart, requiring admission to a hospital for transfusion. His abdomen then began to swell and exploratory laparotomy was performed with the possibility of perforated ulcer evidently in mind. A large volume of ascitic fluid was removed at operation and an omentopexy was performed. During the next four months he required paracentesis every eight to ten days, until January 1942 when a spontaneous remission in the ascites occurred and he was able to return to work. In December of that year he suddenly experienced another massive hemorrhage into the gastrointestinal tract with both hematemesis and tarry stools. Shortly thereafter abdominal swelling recurred. After several transfusions he was strong enough to go to a hospital in Philadelphia where his esophageal varices were injected in an attempt to thrombose them. Two days later he again bled profusely and there was once more hematemesis in January 1943. The patient had been treated for several months outside the hospital on the Patek regimen. In spite of this and the surgical procedures, he required four paracenteses between January and March 1943 when he was admitted to the hospital. The last paracentesis was performed ten days before, yet he was already uncomfortable from abdominal distention at the time of admission. He had lost 20 pounds during the previous six months. There had been no jaundice at any time.

On physical examination the important findings were as follows: moderate pallor without icterus, evidence of weight loss, soft edema about ankles, several vascular "spiders," "liver palms," tongue a beefy red but no papillary atrophy present, lungs clear, bases high, heart pushed upward, split first sound with soft systolic blow at apex, pulse regular, blood pressure 105/55, abdomen hugely distended with shifting dullness and striking fluid wave, pronounced collateral venous circulation over abdomen and lower chest, moderate-sized hemorrhoids. No organs or masses could be felt in the tensely distended abdomen before paracentesis. After tapping the abdomen was soft and relaxed; there was an upper midline scar with a large ventral hernia through which the markedly enlarged spleen protruded like an Aleutian island rising out of the sea. The spleen was very hard, the edge fairly sharp with a distinct notch in the median border, no bruit or friction rub heard over the spleen. A hard nodular liver edge could be felt 4 cm. below the xiphoid in the epigastrium but could not be traced below the right costal margin. Neurologic examination was entirely normal.

Admission impression was Banti's syndrome (due to splenic vein thrombosis) with marked splenomegaly and secondary cirrhosis of the liver although the possibility of primary cirrhosis following exposure to toxic substances years before was considered.

Laboratory Findings: Blood count, red blood cells 3,780,000, hemoglobin 9.3 gm. or 64 per cent, volume packed red blood cells 30.3, leukocytes 3850 with normal differential formula, sedimentation rate 33.0 mm. corrected to 9.0 mm. in one hour. Urine was normal. Serologic test for syphilis was negative. Blood chemistry: nonprotein nitrogen 40 mg. per 100 cc., sugar 112 mg. per 100 cc., serum chloride 110.4 milliequivalents per liter, total serum protein 5.75 gm. with albumin 2.81 gm. and globulin 2.94 gm. per 100 cc. Prothrombin time was 20 seconds compared with control of 15 seconds. Bromsulfalein liver function test

showed 28 per cent retention after thirty minutes. The phenolsulfonphthalein kidney function test showed 95 per cent excretion in two hours, an abnormally high value as is frequently seen in liver disease.

**Clinical Course** The patient was placed under the Patek diet supplemented with yeast, choline and polyvitamin capsules as in the previous cases. The day after admission he vomited bloody fluid. At paracentesis 10 liters of straw-colored fluid was removed with specific gravity 1.014 and practically no cells. Six days later, 7500 cc of fluid were removed. The patient was given a transfusion and on April 6 splenectomy was performed by Dr W. M. Firor under sodium pentothal, nitrous oxide and local anesthesia. The liver was found to be small, hard and nodular, and about one-half normal size. The operator noted several branches of the splenic vein fully 1 cm in diameter. The left coronary vein was ligated with the splenic pedicle. The spleen weighed 840 gm. Microscopic report by Dr S. S. Blackman and Dr R. C. Clay: "The splenic tissue reveals changes which are characteristic of elevated venous tension in the splenic system. These are characterized by dilated venules and splenic sinuses which are now emptied of their blood. There is some fibrosis surrounding these sinuses and the tissues of the pulp seem quite empty. The malpighian bodies are somewhat atrophic." Final pathologic diagnosis was changes in the spleen indicating an increased venous pressure.

The postoperative course was essentially uneventful. Ascitic fluid drained from the abdominal wound for two weeks before the wound closed. The patient was discharged on the seventeenth postoperative day with only a small amount of ascites present. Two weeks later he was readmitted to the Urologic Service with acute postcatheterization cystitis due to staphylococcus. This cleared up rapidly with one week of sulfathiazole therapy. On May 10, 7500 cc of fluid was removed at paracentesis. Since then the patient has been seen in June, August and November 1943, also in March and November 1944. He experienced no further recurrence of ascites, hematemesis or melena. He gained strength and weight and has been able to hold a forty-eight-hour week defense job without difficulty, returning from work in the evenings so full of energy that he frequently takes his wife out to the movies or to dance! By August 1943 his blood count had returned to a perfectly normal level and it has remained normal ever since. The patient has continued to follow the Patek diet supplemented with yeast, choline and vitamin capsules ever since splenectomy. Although his liver remains palpably hard and nodular in the epigastrium, he is to all intents and purposes subjectively "cured" at the time of the present writing, nineteen months after splenectomy.

**Comment**—This 39 year old nonalcoholic man with severe cirrhosis of the liver either primary or secondary to Banti's splenic anemia, who had suffered from repeated hematemesis and recurrent ascites over a twenty-month period in spite of omentopexy, injection of esophageal varices, and a lengthy trial of the Patek regimen, made a dramatic recovery following splenectomy and has remained clinically well with no further ascites, hematemesis or anemia over a nineteen-month period since the removal of his spleen. It would appear that splenectomy was a life-saving measure in this particular instance. Since the liver was found to be about one-half normal in size at operation, the patient was impressed with the importance of continuing on the Patek diet supplemented with yeast and choline. He has followed this regimen religiously and is enjoying excellent health while holding down a full-time defense job at the present writing.

## SUMMARY AND CONCLUSIONS

1 An abundance of experimental and clinical evidence points to dietary deficiency as a most important factor in the etiology of fatty liver and cirrhosis of the liver

2 Treatment of fatty liver and cirrhosis by a nutritious diet high in calories, protein and vitamins, especially the vitamin B-complex, appears to be the most promising form of therapy for this disease, even after signs of hepatic decompensation such as jaundice, ascites and hematemesis have developed.

3 This dietary treatment of cirrhosis has been discussed in some detail along with adjunctive therapeutic measures including various surgical procedures designed to relieve ascites and to prevent hematemesis.

4 Four cases are presented to illustrate the various aspects of dietary therapy. In one of these cases splenectomy was followed by dramatic relief from both ascites and hematemesis

## BIBLIOGRAPHY

- 1 Ratnoff O D and Patek, A. J. *Medicine*, 21 207 1942
- 2 Patek, A. J., *Bull. N Y Acad Med.*, 19 498, 1943
- 3 Wayburn, E. and Guerard, C. R. *Arch Int Med.*, 66 161 1940
- 4 Allan, F N., Bowie, D J., MacLeod, J J R. and Robinson, W L. *Brit. J Exper Path.*, 5 75, 1924
- 5 Frame, E. G. *Yale J Biol & Med.*, 14 229 1941-42
- 6 MacLean D L. and Best, C. H. *Brit. J Exper Path.*, 15 193, 1934
- 7 György P and Goldblatt, H. *J Exper Med.*, 70 185, 1939, and 72 1, 1940
- 8 Rich A. R. and Hamilton, J D. *Bull. Johns Hopkins Hosp.*, 66 185, 1940.
- 9 Rhoads, C. P. and Miller D K., *J Exper Med.*, 67 463 1938
10. Patek, A. J. *Proc. Soc. Exper Biol. & Med.*, 57 329 1937
- 11 Patek, A. J. and Post, J., *J Clin. Investigation*, 20 481, 1941
12. Snell, A. M. *Minnesota Med.*, 23 551 1940
- 13 Fleming R. G. and Snell, A. M. *Am. J Digest. Dis.*, 9 115 1942
- 14 Keefer, C. S. and Fries, E. D., *Tr. A. Am Physicians*, 57 283 1942

# THE USE OF SULFAMERAZINE IN PNEUMOCOCCAL PNEUMONIA

A GENECIN, M D \* AND R A NELSON, M D †

THE desirability of discovering safer and more effective sulfonamide derivatives for the treatment of bacterial infections has led to the recent extensive trials of sulfamerazine by a number of investigators<sup>1-12</sup> A methyl derivative of sulfadiazine, this drug has been shown to be very rapidly and completely absorbed after oral ingestion and relatively slowly excreted, thus making it possible to maintain adequate blood concentrations on smaller or less frequently administered doses Beta-hemolytic streptococcal, meningococcal and pneumococcal infections have already received extensive clinical trial with results which compare favorably with already well-tested sulfonamide drugs The preliminary studies seem to indicate that the toxicity of sulfamerazine is approximately the same as that of sulfadiazine

## CASES INCLUDED IN THIS STUDY

Between January 1943 and June 1944, we have treated 292 cases of lobar pneumonia at the Johns Hopkins Hospital with sulfamerazine with gratifying results We believe that the cases which have come under our observation on the public wards are relatively severe infections For example, 20.9 per cent of the patients were found to have a blood stream infection with a typable pneumococcus at the time of entry Likewise, the incidence of involvement of more than one lobe is 31 per cent Many of our patients had other severe concomitant illnesses which are known to jeopardize the outcome of lobar pneumonia Approximately 15 per cent of the series were chronic alcoholics—a group of patients in whom multiple lobe involvement, bacteriemia, leukopenia, jaundice and delirium are especially apt to occur either singly or in combination Fifty-two patients were admitted with lobar pneumonia at the height of the influenza epidemic in December 1943 These patients were noted to have particularly virulent infections, often associated with leukopenia

A routine attempt to corroborate the clinical diagnosis with direct demonstrations of pneumococci in the sputum was made in almost all instances It is our impression that the direct capsular "quellung" procedure is of the utmost value in confirming the diagnosis of pneu-

---

From the Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

\* Instructor in Medicine, Johns Hopkins University School of Medicine.

† Associate in Medicine, Johns Hopkins University School of Medicine, Assistant Physician, Johns Hopkins Hospital

mococcal pneumonia at the earliest possible moment. Failure to obtain a direct typing from the sputum or from the inoculated mouse peritoneum should awaken a suspicion that the infection may not be primary lobar pneumonia and a re-evaluation of the patient's status is indicated. Thirty-four patients, many of whom had been treated with other sulfonamide drugs prior to entry, had no pneumococci in the sputum. These are included in the present series because the history and clinical course was otherwise typical of primary lobar pneumonia. We have not included influenzal, primary atypical, staphylococcal or streptococcal infections in the study.

#### PLAN OF TREATMENT

The plan of treatment was to give an initial dose of 4 gm. of sulfamerazine by mouth or 5 gm. of sodium sulfamerazine by vein, followed by maintenance oral doses of 3 to 6 gm. a day. In the early part of the study, thirteen of the more severe cases were given antipneu-

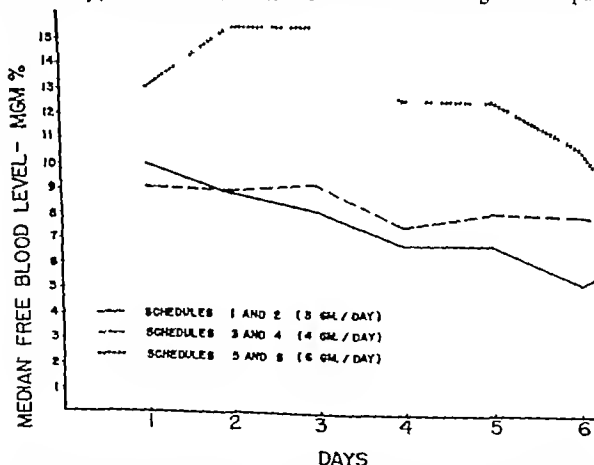


Fig. 47—Median whole blood concentrations of free sulfamerazine observed in 165 patients on a dosage of 3 gm. a day in 62 patients on 4 gm. a day, and 33 patients on 6 gm. a day.

mococcal rabbit serum as supplementary therapy, either because of initial grave prognosis or poor response to chemotherapy. As penicillin became more generally available later in 1943, twenty-two patients were given that drug in addition to full doses of sulfamerazine. Penicillin was given in doses of 20,000 units intravenously or intramuscularly every three hours.

Treatment with sulfamerazine was continued in all cases until forty-eight hours or more after the temperature and clinical response indicated satisfactory control of the infection. It was found that the period of time and total quantity of drug necessary to effect a cure was exceedingly variable. In general, many of those admitted early in the course of the disease had a prompt artificial crisis, but despite the temptation in these cases to discontinue therapy after two or three days, it was thought wiser to continue treatment until the risk of relapse was minimized. Treatment was promptly discontinued on suspicion of toxic reaction. Whenever possible, an oral test dose of 0.5 to 1 gm was given before hospital discharge where febrile and cutaneous sensitivity was suspected.

Blood sulfamerazine determinations were done at frequent intervals by the method of Bratton and Marshall. The median blood levels of free sulfamerazine (whole oxalated blood) on schedules of 3, 4 and 6 gm a day taken by mouth after an initial intravenous or oral dose are shown in Figure 47. As is to be expected, higher and better sustained levels are obtained with the more intensive schedules. With the passage of time, the daily median blood levels on all schedules decrease. On the 3 gm per day schedule, the daily medians vary between approximately 5 and 10 mg per 100 cc, on the 4 gm per day dosage, between 7.5 and 9.5 mg per 100 cc, and on the 6 gm per day, between 10.5 and 15.5 mg per 100 cc.

### TOXIC REACTIONS

The toxic reactions which were encountered were of the same character and approximate frequency observed with other sulfonamide drugs in current use. In Table 1, there is presented an analysis of toxic manifestations in relation to dosage intensity. Fever and/or rash and renal irritation head the list of untoward effects. The rashes were similar to those seen with other sulfonamides, one of the patients developed an erythema multiforme-like syndrome with stomatitis, conjunctivitis and a papulovesicular eruption. Erythema nodosum was not seen. Two patients who developed urinary suppression, flank pain and hematuria were vigorously treated with forced fluids and alkalis and recovered promptly. The routine administration of alkalis in the form of sodium bicarbonate in large doses was not pursued. Although it would appear advisable to maintain a constantly alkaline urine, inconveniently large doses of sodium bicarbonate are necessary. Furthermore, many of the fatal renal reactions which are observed during sulfonamide administration are associated with a widespread toxic reaction in the tissues rather than simple mechanical obstruction by sulfonamide calculi. It is our impression that careful observation of the urinary output together with frequent urine examinations is adequate in most instances.

Nausea and vomiting were exceedingly rare. Delirium was com-

TABLE 1—TOXIC REACTIONS TO SULFAMERAZINE IN 292 PATIENTS TREATED FOR LOBAR PNEUMONIA

Schedule	Irregular		3 Gm. per Day		4 Gm. per Day		6 Gm. per Day		Total	
	32 patients		165 patients		62 patients		33 patients		292 patients	
	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent	No	Per Cent
No toxic reaction	28	87.5	148	89.7	57	91.9	28	84.8	261	89.4
Fever and/or rash	2	6.2	8	4.8	1	1.6	3	9.0	14	4.8
Renal (microscopic hematuria)	0	0	5	3.0	2	3.2	2	6.1	9	3.1
Renal (gross hematuria)	0	0	1	0.6	1	1.6	0	0	2	0.7
Leukopenia	2	6.2	2	1.2	1	1.6	0	0	5	1.7
Gastrointestinal	0	0	1	0.6	0	0	0	0	1	0.3
Percentage of patients with toxic reactions	15.5		10.3		8.1		15.4		10.6	



TABLE 2—ANALYSES OF 292 PATIENTS WITH LOBAR PNEUMONIA TREATED WITH SULFAMERAZINE

	Number of Cases	Number with Multiple Lobes	Number with Concurrent Disease	Bacteremic			Nonbacteremic			Total Deaths
				Number	Complica-tions	Deaths	Number	Complica-tions	Deaths	
Sulfamerazine alone	256	64	108	33	5	7	223	26	7	14 (5.4%)
Sulfamerazine plus serum	13	9	8	9	4	4	4	2	1	5 (38.4%)
Sulfamerazine plus penicillin	22	18	12	19	8	5	3	0	1	6 (27.3%)
Sulfamerazine plus serum plus penicillin	1	1	0	1	0	1	0	0	0	1 (100%)
Totals	292	92	128	62	17	17	230	28	9	26 (8.9%)

monly observed in very ill patients, particularly alcoholics, but was not thought to be related to therapy in any instance. Despite the presence of the methyl group in sulfamerazine, no case of peripheral neuritis was observed, although all investigators have looked for an example of this reaction in view of the structural analogy with sulfamethylthiazole. Leukopenia, although frequent, was never alarming and there were no instances of agranulocytosis. Since the incidence of toxic reactions may be higher with the higher dosage schedules, we recommend a dose of 3 or 4 gm a day.

## RESULTS

Analyses of groups of cases treated with sulfamerazine alone, sulfamerazine plus serum and sulfamerazine plus penicillin are presented. The relatively low incidences of involvement of more than one lobe,

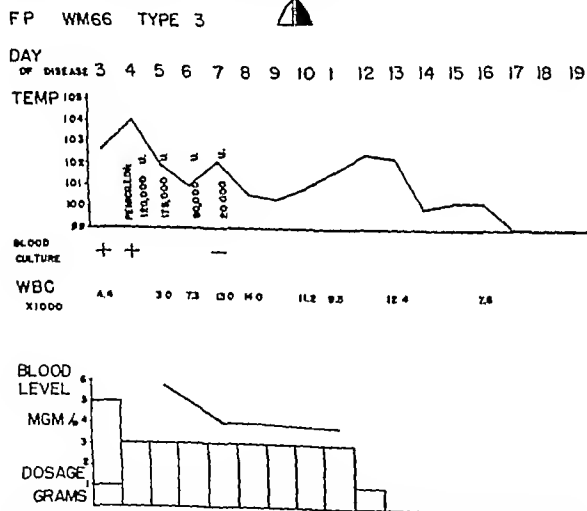


Fig 48.—A gravely ill patient, presenting many unfavorable clinical features, who responded well to the combination of sulfamerazine and penicillin.

concurrent illnesses and bacteriemia in the sulfamerazine group attests to the milder nature of these infections as contrasted with the selected groups of more seriously ill individuals who required supplementary treatment. The most unfavorable group prognostically was the penicillin treated, as is shown by the bacteriemic rate of 86.3 per cent (nine-

teen out of twenty-two) The case fatality rate of 27.3 per cent in this group seems to indicate that penicillin is at least as effective as serum, if not more so, as an adjunct to sulfonamide treatment

The course of treatment in a 66 year old white man with arteriosclerotic heart disease, myocardial insufficiency, bundle branch block, chronic alcoholic addiction and Laennec's cirrhosis with jaundice, who developed type III lobar pneumonia with bacteriemia is illustrated in Figure 48

In the entire series of 292 cases the case fatality rate was 8.9 per cent and the incidence of nonfatal complications was 15.4 per cent It should be mentioned that 15 of the twenty-six deaths occurred within twenty-four hours of entry The case fatality rate, excluding deaths within twenty-four hours after institution of therapy, is 4.0 per cent.

TABLE 3—COMPLICATIONS ENCOUNTERED IN 292 LOBAR PNEUMONIA PATIENTS TREATED WITH SULFAMERAZINE

	256 Cases Without Supplementary Treatment	36 Cases With Supplementary Treatment	Total
Living without complication	211 (82.5%)	10 (27.8%)	221 (75.6%)
Death	14 (5.4%)	12 (33.0%)	26 (8.9%)
Spread	9 (3.5%)	4 (11.1%)	13 (4.5%)
Pleurisy	9 (3.5%)	4 (11.1%)	13 (4.5%)
Empyema	2 (0.8%)	1 (2.8%)	3 (1.0%)
Thrombophlebitis	5 (2.0%)	2 (5.6%)	7 (2.4%)
Lung abscess	0 (0)	2 (5.6%)	2 (0.7%)
Pericarditis	0 (0)	1 (2.8%)	1 (0.3%)
Meningitis	0 (0)	1 (2.8%)	1 (0.3%)
Unresolved pneumonia	6 (2.3%)	2 (5.6%)	8 (2.7%)
Other	3 (1.2%)	3 (8.3%)	6 (2.1%)
Patients with death or complications	45 (17.6%)	26 (72.4%)	71 (24.3%)

Table 3 is a presentation of the distribution of complications encountered Approximately three quarters of all cases had a completely satisfactory outcome The more seriously ill patients, who required supplementary therapy, suffered a combined case fatality and complication rate of 72.4 per cent, whereas this figure for the sulfamerazine group is only 17.6 per cent Spread of the infection and the pleurisy

were observed as the most common complications. More serious complications were rare.

#### SUMMARY

1 An analysis of 292 cases of lobar pneumonia treated with sulfamerazine, either alone or in combination with antipneumococcal serum or penicillin, is presented

2 It is concluded that sulfamerazine is both a safe and effective chemotherapeutic agent in the treatment of lobar pneumonia

#### BIBLIOGRAPHY

- 1 Welch, A. D., Matus, P. A., Larven, A. R., Benson, W. M. and Shiels, E. H. *J. Pharm. Exp. Ther.*, 77:357, 1943
- 2 Clark, J. K., Flippin, H. F. and Murphy, F. D. *Am. J. Med. Sc.*, 205:717, 1943
- 3 *Ibid.*, p. 846
- 4 Geffer, W. L., Rose, S. B., Dornan, A. H. and Flippin, H. F. *Am. J. Med. Sc.*, 206:211, 1943
- 5 *Ibid.*, p. 216
- 6 Hageman, P. O., Harford, C. G., Sobin, S. S. and Ahrens, R. E. *J.A.M.A.*, 123(6):325, 1943
- 7 Hall, W. H. and Spink, W. W. *J.A.M.A.*, 125(3):125, 1943
- 8 Lepper, M. H., Sweet, L. K. and Dowling, H. F. *J.A.M.A.*, 123(3):134, 1943
- 9 Lepper, M. H. and Stanley, E. D. *Med. Ann. District Columbia*, 13:54, 1944
- 10 Annotation. *Lancet*, 2(25):773 (Dec. 18), 1943
- 11 Anderson, O. G., Oliver, C. S. and Keefer, C. S. *New Eng. J. Med.*, 230:369, 1944
- 12 Dowling, H. F. *Med. Ann. District Columbia*, 12:468, 1943

# THIOURACIL AND HYPERTHYROIDISM

ELLIOT V. NEWMAN, M.D.\*

THE discovery, experimental development and clinical application to hyperthyroidism of thiouracil has stimulated inquiry into the physiology of the thyroid gland and a hope that the disease can be controlled by medical treatment. Dissatisfaction with previous methods of treatment has been widely expressed. While proving a tremendous advance in the control of the disease and preparation of the patient for operation, iodization is not completely satisfactory. Though most patients respond well to iodine therapy, there are some who respond only partially and a few who do not respond at all. Furthermore, continuation of iodine treatment does not prevent exacerbations. It has been emphasized that the natural history of the disease is one of remissions and exacerbations, perhaps finally "burning itself out," which is not fundamentally altered by temporary control with iodine. Thus the usual course of treatment is to remove most of the gland surgically to effect a permanent remission<sup>1, 2</sup>.

Thyroidectomy has been adversely criticized for several reasons as a treatment for hyperthyroidism. Operative treatment is sometimes followed by complications or failures. Besides the small risk of anesthesia and usual complications of a surgical operation, there is the possibility of postoperative "thyroid storm." A rare case may result in parathyroid tetany or paralysis of the vocal cord. More serious is the late occurrence of undetected postoperative myxedema. But the greatest objection to surgical interference is that, somewhat like iodine treatment, it sometimes fails to cure the patient. Too often improvement after thyroidectomy is temporary and the disease reappears later. It thus pursues its "natural course" and produces an exacerbation, or "burns out" and causes myxedema.

In the "burning out" process the small amount of tissue left by the surgeon may become inadequate to maintain normal metabolism. Thus a patient who has thyroid disease must be considered a patient throughout his life because the manifestations of the disease are variable and protracted. Also there is a group of patients who may be made worse by operation, for it may precipitate a progressive increase in exophthalmos, resulting in ophthalmoplegia and disastrous ocular complications.

Lastly, there is the objection to thyroidectomy that it is a crude

---

From the Medical Clinic, The School of Medicine, Johns Hopkins University and Hospital, Baltimore, Maryland.

\* Instructor in Medicine, Johns Hopkins University School of Medicine, Resident in Medicine, Johns Hopkins Hospital.

'unphysiological' method of attacking a disease, the pathological physiology of which has been extensively studied. In other words, it seems reasonable in the light of what is now known, that inevitably the treatment must be based upon more sound physiological and biochemical principles.

Granting that thyroidectomy is not a completely satisfactory treatment in the usual case, there are certain types in which operation is indicated. Very large goiters are removed because of cosmetic reasons and local constriction of other organs of the neck. Adenomas of the thyroid may be precancerous. Also, some patients because of mental or social factors may be unable to carry out any medical regimen. When serious toxic reactions occur, due to medical therapy, one must resort to operation.

With the advent of thiouracil in the treatment of hyperthyroidism, it was hoped that the disease could be controlled during the active stage throughout its history and that patients who required operation could be better prepared. From the standpoint of insight into the fundamental processes of the disease, thiouracil opened a new approach. It is interesting, therefore, at this time to review briefly the discovery, experimental development and clinical application of thiouracil in order to assess its place in the therapy of hyperthyroidism.

#### DISCOVERY AND EXPERIMENTAL DEVELOPMENT

Substances which produce goiter were known before the discovery of thiouracil. Rabbits fed a cabbage diet were found to develop huge glands.<sup>16</sup> Thiocyanate administered to animals and to man occasionally produced enlargement of the thyroid.<sup>17</sup> This type of goiter could be abolished by the administration of iodine.<sup>18</sup>

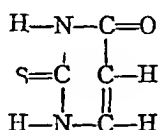
A new group of substances of which thiouracil is one whose action was not abolished by iodine administration was discovered in several ways. Kennedy and his associates found that a diet of Brassica seeds fed to animals caused a delay in growth, enlargement of the thyroid gland with hyperplasia of the epithelium and loss of colloid. The pituitary glands of these animals showed increase in basophil cells. The hyperplasia could be abolished by hypophysectomy or by administration of thyroid extract, but not by iodine. Later Kennedy reported that allylthiourea produced the same changes.<sup>4, 5</sup>

Also Richter noted when feeding phenylthiocarbamide to rats that prolonged dosage caused enlargement and hyperplasia of the thyroid.<sup>6</sup> At about the same time the Mackenzies while testing the antibacterial effects of sulfonamides on rats found incidentally that there was great enlargement of the thyroid glands. Subsequent investigation showed that sulfonamides and thiourea compounds all produced lowering of the basal metabolic rate, enlargement of the gland with loss of colloid, increase in the height of the epithelium and 'thyroidectomy' cells in the pituitary gland. The effects on the thyroid gland were

abolished by thyroxin administration, hypophysectomy, but *not* by giving iodine <sup>7</sup>

Further work on the mechanism of action on the thyroid gland of the sulfonamides and thiourea compounds by Astwood finally led to the selection of thiourea and thiouracil for clinical use in the treatment of hyperthyroidism <sup>8, 9</sup> Astwood tested over one hundred related compounds of different chemical structure to compare their activity and toxicity The compounds fell into two groups, (I) the thiourea derivatives and (II) the aniline derivatives The chemical structure essential for activity in Group I was HN CS NH, for Group II, NH<sub>2</sub> C<sub>6</sub>H<sub>4</sub> The entire structure of the first group was necessary, activity was lost if the S or either NH radical was replaced In Group II the amino group must be free The most active substance in Group I was thiouracil, in Group II the aminobenzoic acids

The formula for thiouracil is,



From these earlier investigations a theory of the mechanism of action of thiouracil was derived It was postulated that thiouracil interferes with the manufacture of thyroid hormone by the gland This resulted in a diminished secretion of hormone which was followed by lowering of basal metabolic rate, failure of growth and development, and lowered food intake Reduction of the secretion of thyroid hormone elicited an increased output of pituitary thyrotropic hormone with histologic changes in the pituitary Thyrotropic hormone then stimulated the thyroid gland, causing hyperplasia with heightening of the epithelium and enlargement, and loss of colloid A rather paradoxical picture of a myxedematous animal with a highly overactive appearing thyroid gland is the result of the chain of events initiated by the action of these drugs <sup>10, 11, 12, 13, 14, 15</sup>

Since the work on the primary metabolic and histologic effects of thiouracil and related compounds there has been much experimental data on the metabolism of iodine in the thyroid gland in the intact organism and in isolated tissue The level of protein bound iodine in plasma is known to be correlated closely with the basal heat production of the organism <sup>18</sup> In hyperthyroidism the level is elevated and after treatment with thiouracil the level falls, demonstrating directly the lowering of the amount of hormone due to the drug The mechanism within the thyroid gland whereby the hormone production is depressed has not been completely elucidated Studies with injections of radioactive iodine have shown a marked inability of the thiouracil treated gland to utilize the iodine, most of the iodine being excreted in the urine The concentration of iodine found in the gland after

administration of thiouracil is very low. This result is in contrast to the normal gland which takes up considerable quantities of administered iodine, and it is in marked contrast to the glands made goitrous with thiocyanate which have a great avidity for administered iodine. Not only is there a decreased uptake of iodine by the gland, but the conversion of iodine to diiodotyrosine or organically bound iodine is markedly depressed. This has been demonstrated in the intact gland and in tissue slices. In tissue slices, however, the iodine concentrating power may not be depressed although conversion to hormone is greatly inhibited.<sup>19 20 21, 22, 23 24 25 26</sup>

The marked decrease in iodine in the thyroid glands due to thiouracil is promptly reversible within one to two weeks after discontinuing the drug. That the decrease in iodine in the gland was due to thiouracil and not to thyrotropic hormone is shown by the relatively small loss of iodine after large injections of thyrotropic hormone.

The exact mechanism of action of thiouracil in the thyroid gland has not yet been elucidated. It was demonstrated in vitro that thiouracil inhibits the peroxidase activity in thyroid tissue which would interfere with the conversion of diiodotyrosine to thyroxine.<sup>27</sup>

There are interesting observations on other effects of thyroid hormone, iodine, thiouracil and thyrotropic hormone, and of the modifying action of one substance on the other. This may have bearing on the therapy in hyperthyroidism since more than one form of therapy may be given simultaneously or one may follow the other. Thyrotropic hormone given with thiouracil enhances the goitrogenic effect. Thyrotropic hormone alone causes marked enlargement of the thyroid gland but causes relatively little loss of iodine from the gland. Potassium iodide inhibited the colloid depleting effect of thyrotropin where thyrotropin was given alone or in conjunction with thiouracil. This effect of potassium iodide may be of therapeutic value since a gland with more colloid may be firmer and easier to remove surgically.

The influence of thyroid hormone and potassium iodide upon the storage of thiouracil in the thyroid gland has been investigated. Thyroid hormone decreases thiouracil storage, whereas potassium iodide greatly increases storage of thiouracil in the gland. It has been suggested that iodine administration might enhance the effect of thiouracil because of increased storage of thiouracil.<sup>28 29 30</sup>

One might reasonably expect that a combination of iodine and thiouracil would cause a more rapid fall in basal metabolic rate than either alone, since both will cause a rapid remission of hyperthyroidism and a fall in blood hormonal iodine. However, it appears that there is a maximum rate at which metabolism can be lowered by attacking the thyroid gland either chemically or surgically. Means observed that the maximum rapidity of decline of the basal metabolic rate is the same whether the patient with hyperthyroidism is iodinated or thyroidectomized, or when the myxedematous person is allowed to decay. In



one person identical curves of decline in metabolism were produced by iodination when the person was spontaneously thyrotoxic and by cessation of thyroid administration when she was artificially thyrotoxic. From these facts it seems apparent that there is a definite limitation to the rapidity of response of a thyrotoxic individual no matter what therapy be used. The gland may be cut off physiologically or surgically and whatever hormone remains in the body requires a definite time to catabolize. According to this view, iodine administration stops delivery of hormone from the gland to the body, but does not cause storage in the gland of hormone already secreted. It is not likely, therefore, that thiouracil alone or in combination with other drugs will cause a lowering of metabolism faster than the normal catabolism of thyroid hormone will allow.<sup>31</sup>

#### CLINICAL APPLICATION OF THIOURACIL

**Pharmacology**—The absorption, distribution and excretion of thiouracil has been studied by Williams, Weinglass and Kay.<sup>32</sup> Absorption from the gastrointestinal tract is very rapid. The blood level rises within the first hour after a single dose of 0.2 gm. and falls steadily and is very low after eight hours. Thereafter a small amount is present for two days. When 0.2 gm. were given every four hours for three days the blood level remained fairly constant after twenty-four to forty-eight hours at 2 to 3 mg. per 100 cc. of blood. With oral administration of a total of 0.2 to 1.2 gm. a day given in doses of 0.2 gm. at evenly spaced intervals, the blood level ranged from 0.8 to 6.4 mg. per 100 cc. Most of the drug is carried in the red blood cells. The renal excretion remains relatively constant during this period. Destruction of some of the drug occurs in the gastrointestinal tract and some by the rest of the body. No thiouracil is excreted in the stools. It does not accumulate to any great extent in the body even in a patient with nephritis or cirrhosis of the liver because many tissues can apparently destroy the drug. The drug is distributed throughout all body tissues that have been examined at autopsy. Relatively large quantities were sometimes present in bone marrow, thyroid, ovaries and pituitary. In two patients with nodular thyroid glands removed at operation the analyses of the adenomatous tissue showed markedly higher concentration of thiouracil than the surrounding relatively normal tissue.

It is apparent that the rapidity of absorption and excretion of the drug requires that it be given in divided doses throughout the day. The dose used for clinical purposes has been from 0.1 to 1 gm. per day. The usual practice is to give 0.6 gm. per day for a few weeks or until the metabolism is controlled and then maintain the patient on 0.1 to 0.4 gm. per day. Evidence has been presented that the daily maintenance dose must be adjusted to the individual since some may not be controlled by low dosage, while others may develop signs of myxedema on larger amounts.

**Toxicity**—Animal experimentation has shown thiouracil to be relatively nontoxic. Examination of patients who were given thiouracil before death showed no gross or microscopic pathological lesions attributable to the drug<sup>33 34</sup>

Clinically, however, a variety of toxic effects have been noted, the most serious being *leukopenia* or *agranulocytosis*. Scanning the reports in the literature at present available, there were toxic reactions noted in forty-seven of 377 patients (12 per cent) who received the drug. The most common reactions were fever in fourteen cases, leukopenia in thirteen cases, urticaria or other rashes in eleven cases, and agranulocytosis in five cases. Several patients had combinations of symptoms such as rash, fever and agranulocytosis, or rash and fever. Miscellaneous toxic reactions, some of which were questionably due to thiouracil, were headache, jaundice, enlarged lymph glands, diarrhea, enlarged salivary gland, arthralgia, dental abscesses, gastric distress, nausea vomiting and chills. In one case there was hemorrhage into the thyroid gland supposedly caused by increased vascularity due to thiouracil. A few cases of edema of the legs were reported which might have been due to a salt-retaining effect of thiouracil. In addition, under the heading of toxicity might be listed several cases which showed signs of hypothyroidism on higher maintenance dosages.

Practically all the toxic reactions were found to subside on discontinuing the drug. It was the experience of many investigators that some milder reactions would subside without discontinuing the drug. Also, many reactions did not recur on resuming therapy.

The one toxic effect which has proved very serious and warrants complete cessation of thiouracil therapy is neutrophilic leukopenia or agranulocytosis. Deaths from agranulocytosis have occurred. The attention of clinical investigators has been brought to the fact that thiouracil has been given in about 2000 cases and there have been at least seven fatalities from agranulocytosis. This result imposes certain limitations on the use of the drug. Many other cases of agranulocytosis have occurred but the patients have recovered on the withdrawal of thiouracil<sup>35-36</sup>

The toxic reactions resulting from thiouracil are similar to those complicating sulfonamide therapy. In this connection it is interesting to note the work of Sebrell and his co-workers on the prevention of experimental agranulocytosis in rats given sulfonamides with liver preparations<sup>37</sup>. More recently Goldsmith has found that the neutrophilic leukopenia obtained by feeding thiourea to rats could be prevented by simultaneous feeding of a solubilized liver preparation<sup>38</sup>. One might wonder whether further information obtained on the mechanism of thiouracil and sulfonamide agranulocytosis might not obviate this most serious objection to the use of these drugs.

It is obviously of paramount importance in the treatment of a patient with thiouracil to observe closely the total white cell and dif-

ferential count of the blood Difficulty in interpretation of the values may arise because of the tendency of hyperthyroid patients to have a slight leukopenia with a low percentage of neutrophils It would seem a wise policy to follow the leukocyte count at daily intervals if the total count is as low as 4000 or the differential count shows a fall of neutrophils to 40 per cent, and to discontinue the drug if the total count declines to 3500 or the differential to 30 per cent neutrophils

*Results of Treatment—Prolonged Treatment without Operation—*Very few reports are available on the preoperative preparation of patients with thiouracil Most of the cases are treated without operation in the hope that by controlling the disease as long as it is active a permanent remission may finally be obtained It is apparently too early to judge the success of this procedure since cases have been followed for relatively short periods Of great concern in the long term treatment is the possibility of toxic reactions and the necessity of close observation It is generally agreed that the disease can be controlled as long as the drug is used in adequate doses Exacerbation of the disease is the rule when thiouracil is discontinued However, Astwood has reported nine cases of sustained remissions for as long as two to nine months after discontinuing therapy<sup>37</sup>

*Preoperative Treatment with Thiouracil—*Regardless of whether long term treatment is practicable, it seems fairly certain that thiouracil will have a definite place in the preparation of the thyrotoxic patient for operation The completeness and certainty of the response to thiouracil, and the depletion of a thyroid gland of hormone at the time of operation, are practical advantages

A series of patients with thyrotoxicosis were prepared for operation with thiouracil at the Johns Hopkins Hospital in order to determine its usefulness Previously it had been the policy to prepare patients for operation on the Medical Wards by iodimization and routine supportive measures The patient was then transferred to the Surgical Service when, in the combined judgment of both physicians and surgeons, the patient was adequately prepared This policy was continued with thiouracil preparation

So far thirty-four consecutive cases have been treated Twenty-nine patients had diffuse toxic goiters, four had adenomatous glands and one had carcinoma proved by histological examination

The patients were given a high vitamin, high caloric diet Small doses of phenobarbital were used for sedation Respiratory isolation was usually maintained Before specific therapy was begun two basal metabolic rate determinations were obtained The course was followed by studies of the metabolic rate and by determination of blood cholesterol once or twice weekly The weight, general symptomatology, and size and consistency of the thyroid gland were noted Leukocyte counts and differential counts were done twice weekly and more often if slightly below normal In most cases, through the cooperation of

the ophthalmological service, the degree of exophthalmos was measured objectively with the exophthalmometer before the treatment and after operation.

The first six cases were prepared with thiouracil alone, thereafter patients received thiouracil and iodine simultaneously. The usual dose of thiouracil was 0.6 gm. daily, divided in three doses throughout the day. Iodine was given in the form of Lugol's solution 1.5 cc. daily at different times than the thiouracil. Drug therapy was discontinued the day of operation.

Decision about the preparedness of the patient depended upon the subsidence of symptoms such as nervousness and weakness, upon the subsidence of the metabolic rate, the gain of weight, rise in cholesterol and diminution of the tachycardia. While there is great interest in the rate of fall and extent of fall of the metabolic rate under treatment, the general condition of the patient and other signs were equally important criteria in the decision.

The average metabolic rate of the patients before drug therapy was plus 55 per cent (range plus 14 to plus 90). After an average of twenty-six days (range ten to forty-four days) of thiouracil (with or without iodine) the metabolic level averaged plus 18 per cent (range minus 8 to plus 35). Within five to ten days after operation the average metabolic rate was plus 9 per cent (range minus 25 to plus 25).

Although the average duration of drug therapy was twenty-six days the patients remained in the hospital for longer periods. From two to seven days were required for control observations before treatment. The patients were discharged from the hospital within five to ten days after operation to be followed in the dispensary.

Weight gain was usually steady beginning within a few days of treatment. Nine patients showed no gain or loss. The average weight gain for all patients was 6 pounds (range 0 to 20). Frequently a loss of several pounds occurred in the first few days after admission to the hospital. This is interpreted as a loss of water at bed rest.

A fairly steady fall in the pulse rate took place with treatment. The average of the daily maximum and minimum pulse rate from four-hour charts were plotted and the fall in pulse level was estimated from the graphic curves. The average drop in pulse rate was 14 points (range 0 to 30). Only two patients failed to show a significant fall in pulse rate.

Blood cholesterol rose in a consistent curve as the metabolic rate fell. The average increase of the blood cholesterol over the level obtained before treatment for all patients was 79 mg. per 100 cc. (range 0 to 200 mg.). Four patients failed to show a significant increase.

Serious difficulty with leukopenia or agranulocytosis was not encountered. The average of the lowest leukocyte counts for each patient was 5968 per cu. mm. Seven patients had counts at some time below 5000 but only one patient fell below 4000. No dangerously low percentages of granulocytes occurred.

Objective measurements of the degree of exophthalmos and particularly of any change in exophthalmos under therapy are important because of the possibility of precipitating progressive exophthalmos. Measurements by exophthalmometer were taken in eighteen patients before treatment and in ten patients both before and after treatment. There were no marked increases or decreases in exophthalmos. The changes were within 1 to 3 mm of exophthalmos. Six of the ten patients showed a decrease with treatment, but on the whole the magnitude of the changes were not definitely significant.

Care was taken to anticipate progressive exophthalmos because of other reports of its occurrence with thiouracil and the danger of thyroidectomy in such cases. Excellent descriptions and discussion of this complication of hyperthyroidism have recently been given. Mulvany has recently presented the subject of exophthalmos of hyperthyroidism and the mechanism, pathology and symptomatology of two varieties which he terms "thyrotoxic exophthalmos" and "thyrotrophic exophthalmos," the latter being the "progressive" or "malignant" type which leads to ophthalmoplegia. The fact that the exophthalmometer measurements in the cases in our study remained stationary or tended to diminish is evidence that those cases were of the "thyrotoxic" variety which according to Mulvany are made worse by thyroid hormone, whereas the thyrotrophic variety is improved by thyroid hormone.<sup>59, 60, 61, 62</sup>

*Effect of Iodine Administration before and during Thiouracil Therapy*—The general experience seems to be that previous iodine administration delays the response to thiouracil. Astwood reports some delay but the effect was not consistent.<sup>67</sup> In the present series seven patients had had iodine treatment up to the time of, or to within two weeks before thiouracil therapy. While some of the patients showed a delayed response to thiouracil, the delay was no greater than observed occasionally in patients who had had no iodine previously. Some of the iodine treated patients responded as rapidly as those previously untreated.

The first six patients treated with thiouracil alone proved at operation to have very vascular and friable glands. This led to difficulty in handling the gland and obtaining hemostasis.<sup>68</sup> Because of this unsatisfactory aspect of thiouracil preparation the remainder of the patients were given iodine and thiouracil simultaneously. Since that time the glands have been generally firmer, less vascular and easier technically to remove.

*Postoperative Course*—In no case was there any serious operative or postoperative complication attributable to an increase or an exacerbation of thyrotoxicosis. In nineteen of thirty-four cases the temperature and pulse were equal to or below the preoperative levels within twenty-four hours after operation. In the remaining fourteen cases slight temporary temperature elevations occurred. No patients had fever for

more than forty-eight hours after operation. Fever was most frequently associated with hoarseness and tracheobronchitis. No other causes of fever could be found. Elevations of pulse rate out of proportion to the temperature rise did not occur. One patient developed a hematoma in the wound which subsided uneventfully. Two patients developed unilateral vocal cord paralysis, one of which subsequently remitted. One patient had hypocalcemia which was controlled by calcium administration. On the whole the postoperative course of these patients was uneventful and entirely satisfactory. Follow-up of the patients after discharge from the hospital is still in progress.

### ILLUSTRATIVE CASES

A few illustrations of the preoperative and postoperative course of these patients are appended. Operations were performed by Dr. Alfred Blalock, Surgeon in Chief, and the Resident Staff, Drs. Kenneth L. Pickrell, William P. Longmire, Jr., Herbert E. Sloan, Jr., and George W. Duncan. Pathological sections were examined by Dr. Sam S. Blackman, Jr., Associate Professor of Pathology. The author is indebted to Dr. Alfred Blalock for advice and encouragement, and permission to use the surgical records. Thiouracil was supplied by the Lederle Laboratories, Pearl River, New York.

#### Case 1 Preparation with Thiouracil Alone in a Patient Who Had Previously Received Iodine

C. S., a 25 year old colored woman, was admitted on December 10, 1943 with the chief complaints of nervousness and swelling in neck for several months.

The present illness began with insomnia a year before admission. The patient noticed nervousness and a tremor of the body for five months. There was an increase in appetite but a weight loss of 18 pounds in six months. Her physician gave her Lugol's solution, 10 drops daily for six weeks, until two weeks before admission, and because of lack of improvement in symptoms she was sent to the hospital.

Physical examination on admission showed a thin colored female who was very excitable and fidgety. The temperature was 100° F., the pulse 140, respiration 24 and blood pressure 130/60. The skin was warm and moist. Exophthalmos was visible, and there was slight lid lag and edema of the upper lids. The thyroid gland was visibly and palpably diffusely enlarged, soft with a palpable and audible bruit. The lungs were not remarkable. The heart showed slight enlargement to the left with a rapid rate and a soft systolic precordial murmur. Abdominal, pelvic and rectal examinations were not remarkable. There was a fine tremor of the hands and feet.

Laboratory examinations showed a negative serological test for syphilis. Blood red cell count was 3.8 million, hemoglobin 12.5 gm., hematocrit 39 per cent. Cells after treatment rose to 5 million red cells, 13.6 gm. hemoglobin and 43 per cent hematocrit. Leukocytes remained between 7400 to 12,000 with normal differential counts. Urine and stool examinations were not remarkable.

Other studies were: venous pressure 110 mm. of saline; circulation time (arm to tongue) 8 seconds; chest plate—lungs clear; heart slightly enlarged to left; urea clearance 70 per cent of normal; electrocardiogram not remarkable except for tachycardia.

Exophthalmometer measurements were before treatment—right 22 mm, left 22 mm, after treatment—right 22 mm, left 20 mm

The patient's course is illustrated by the chart (Fig 49) There was loss of nervousness, tremor and weakness No significant change in the size of the thyroid gland was noted, but it seemed to be more firm after treatment

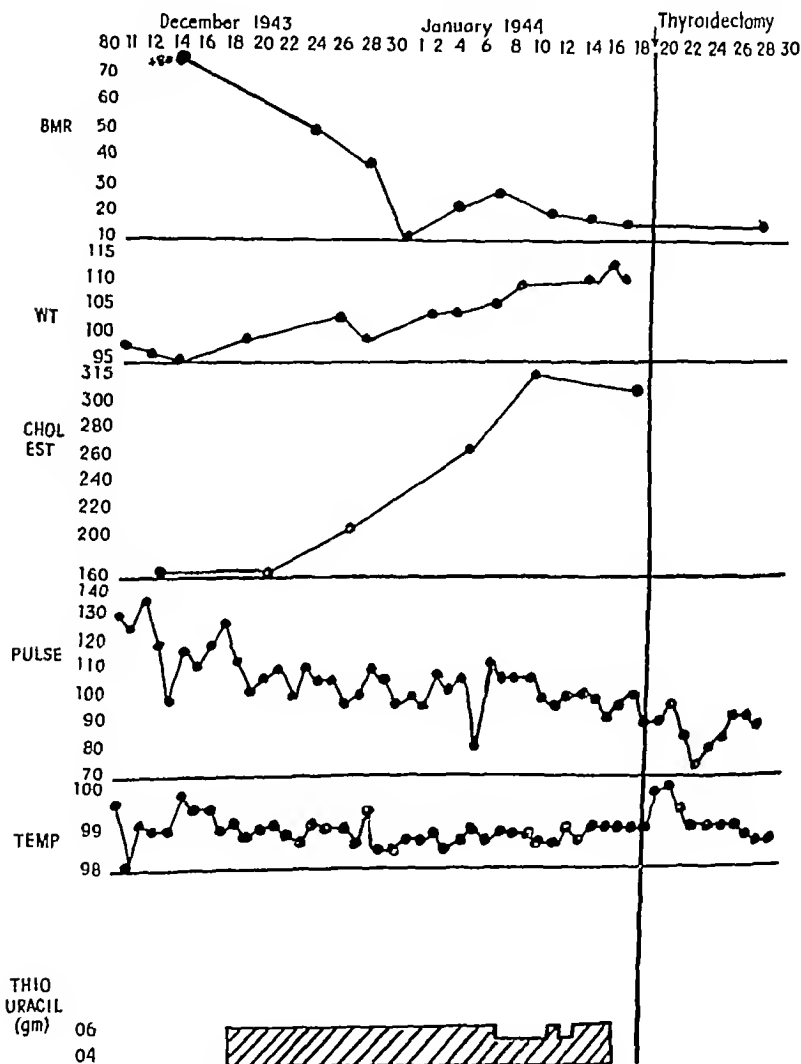


Fig 49—Clinical course in Case I

Subtotal thyroidectomy was carried out. The procedure was extremely bloody. It was difficult to maintain hemostasis because of the marked vascularity and friability of the gland. The operative field was dry at the end of operation, however, and the patient returned to the ward in good condition. Because of loss of blood at operation and fall in blood pressure, she was given a transfusion during operation and another on return to the ward. In the afternoon after operation the pulse was 76 and blood pressure 122/78. Thereafter the course was uneventful except for some hoarseness and soreness at the operative site.

Pathological examination of the removed tissue showed very marked and diffuse hyperplasia with tall columnar cells with loss of colloid. The weight of the removed thyroid tissue was 100 gm. In many places the acini were completely occluded by overgrowth of cells. The gland had the appearance of an untreated case before the days of iodine preparation.

### Case II Preparation of Patient with Iodine and Thiouracil Simultaneously, Who Had Not Received Iodine Previously

C. N., a 33 year old white woman, was admitted with the chief complaints of weakness, nervousness and palpitations for three weeks.

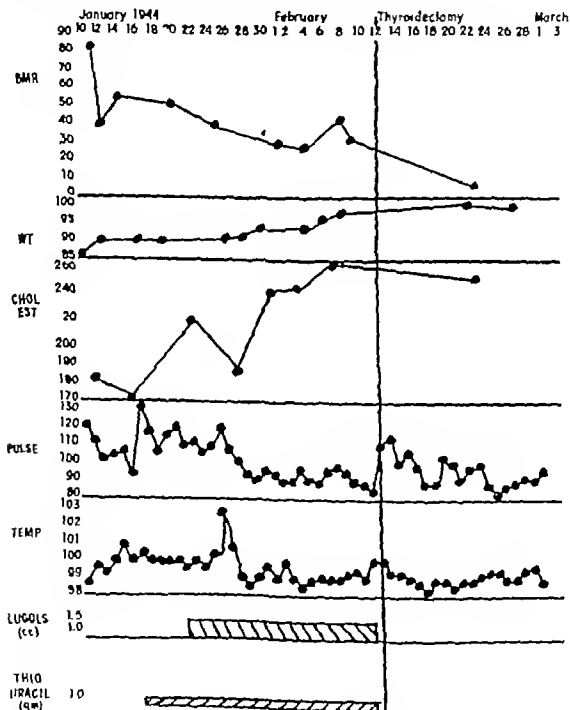


Fig 50—Clinical course in Case II

Past history reveals that six years ago she developed weakness, tiredness, weight loss and nervousness. Enlargement of the neck and prominent eyes were noted. She had a subtotal thyroidectomy at that time in North Carolina. She experienced great improvement and continued in good health until one year ago.



Present illness began about one year ago with fatigue and instability of emotions. She became suddenly much worse three weeks before admission with weakness, palpitation, nervousness and attacks of profuse sweating. Also there had been several attacks of "weakness and numbness" in the extremities, lasting about five minutes.

Physical examination on admission showed a temperature of 99.6° F., pulse 110 and blood pressure 135/72. The patient was a thin nervous woman with prominent staring eyes. The skin was moist. The lid slits were widened. The thyroid gland was diffusely enlarged on both sides and moderately firm with no audible bruit. Scar from previous operation was present. The lungs revealed only slight dullness at the left base. The heart showed a systolic murmur over the precordium and tachycardia. The size was normal. The abdomen was not remarkable. The extremities had overactive reflexes.

Laboratory examinations revealed a normal blood cell picture. The leukocyte counts remained between 7050 to 9800. Urine examinations were normal.

Other studies were x-ray and fluoroscopy of chest—slight thickened pleura in left lower lung fields, normal cardiac outline, no substernal thyroid, venous pressure 95 mm saline, circulation time (arm to tongue) 8 seconds.

Exophthalmometer readings were 21 and 18 mm on the right and left eyes before treatment, and 18 mm in both eyes after treatment.

The patient had a temperature elevation to 103° one day which was unexplained and subsided rapidly. Although the basal metabolic rate (Fig 50) did not fall below plus 25 per cent, the other signs of improvement were dramatic with the gain in weight, increase in blood cholesterol and the slowing of the pulse rate. The patient felt much improved. The gland became firmer.

Operation was somewhat difficult because of scarring due to the previous operation. The gland was firm and gray and did not bleed profusely. The patient stood the procedure well. The tissue removed weighed 88 gm.

The postoperative course was uneventful except on the fourth hospital day when the patient complained of numbness and tingling in the extremities. Blood calcium was 7.0 mg per 100 cc. She was given calcium chloride and calcium lactate by mouth. The paresthesias disappeared and the blood calcium level was 8.3 mg per 100 cc on discharge.

Pathological examination of the tissue showed many acini filled with colloid with cells of low cuboidal type. Other areas were quite hyperplastic with high columnar cells.

### Case III Adequate and Uncomplicated Response to Simultaneous Iodine and Thiouracil Therapy No Previous Iodine

E. J., a 50 year old colored woman, was admitted with the chief complaint of a goiter of three years' duration.

The present illness started with people calling her attention to swelling in the neck three years ago. It caused no symptoms. A year ago she noticed nervousness, increase in appetite and weight loss. She had swelling of the ankles after long standing and became quite weak. The symptoms gradually became worse and she lost 45 pounds. Dyspnea on moderate exertion developed.

Physical examination showed a temperature of 100.2° F., pulse 128 and blood pressure 144/64. The patient looked emaciated, was fidgety and apprehensive. The skin was warm and moist, especially the palms and soles. The eyes showed poor convergence and lack of wrinkling of forehead on upward gaze. The neck showed a markedly enlarged thyroid, firm and slightly nodular. The lungs were clear. The heart was enlarged to the left with a visible precordial pulsation. There was a loud systolic murmur over the precordium and at the apex. Abdominal examination revealed the liver palpable one fingerbreadth below the costal

margin Pelvic and rectal observations were normal There was a tremor of the hands.

Laboratory work showed a normal blood cell picture, the leukocytes remaining between 8200 to 11,000 The urine was normal

Other studies were x ray of chest—the heart was enlarged mostly to the left, lungs clear no substernal thyroid total serum protein 6.31 gm per 100 cc.; electrocardiogram—normal record except for tachycardia

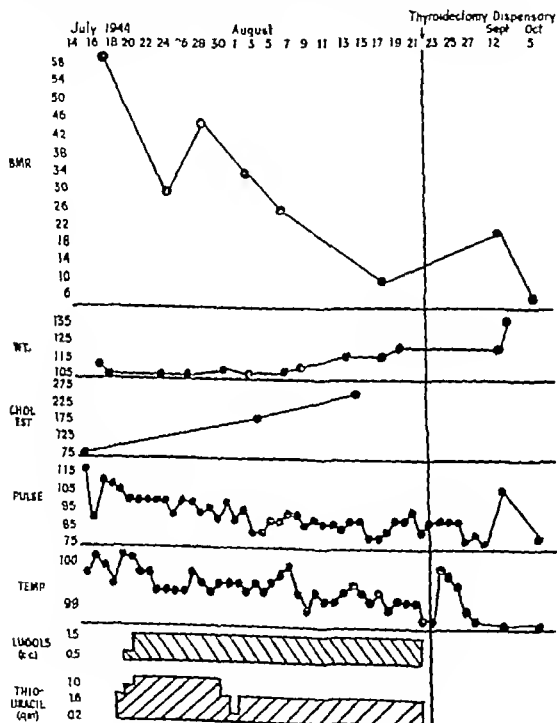


Fig 51—Clinical course in Case III

Exophthalmometer measurements were 20 mm right, 21 mm left before treatment 20 mm right, and 18 mm left eye after treatment

The patient's course was one of steady improvement (Fig 51) The thyroid gland seemed to become definitely smaller under treatment

At operation a firm, whitish gland was found No technical difficulty was encountered The postoperative course was entirely uneventful except for a

period of one-half hour during the first day when the pulse was said to be 110 and irregular. This apparently subsided spontaneously and the pulse was 85 per minute six hours after operation.

Pathological examination of the removed tissue showed *diffuse moderate hyperplasia*. There was no adenoma. The tissue weighed 55 gm.

#### Case IV Preparation with Thiouracil for Thirty days and Iodine in Addition for the Last Fifteen Days

E. P., a 44 year old colored woman, was admitted with the chief complaints of "goiter," weight loss and nervousness.

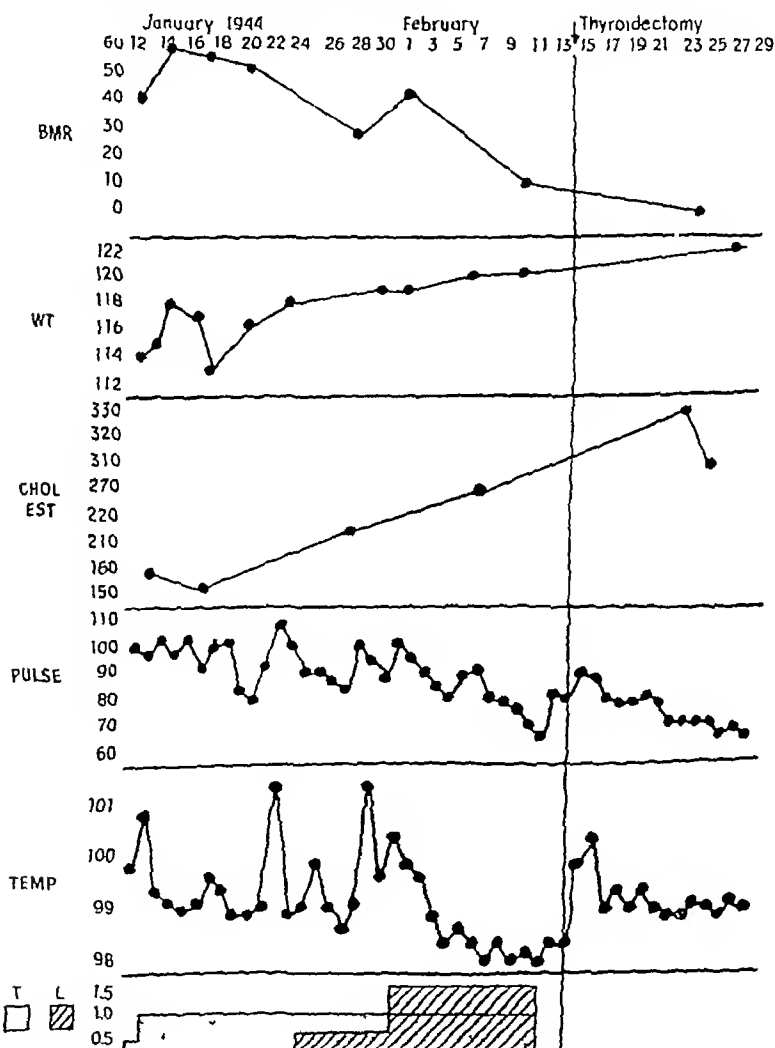


Fig 52—Clinical course in Case IV

The present illness began about six months before admission with nervousness, sleeplessness and feeling warm all the time. Swelling of the neck was noted for four months, and her eyes became prominent. Weakness in the legs became marked. Appetite was increased. She lost 27 pounds in the course of the illness.

Physical examination showed a temperature of 98.6 F., pulse 98 and blood pressure 184/90. The patient was moderately well nourished but nervous and "jumpy" with quick speech and spontaneous laughter. The skin was warm and moist. The lid slits were widened but no other eye signs were made out. The tonsils were large. The thyroid gland was diffusely enlarged to about three times normal size. It was soft and a bruit was heard. The lungs were clear. The heart seemed enlarged to the left. There were soft systolic murmurs at the apex and pulmonic areas. Abdominal, pelvic and rectal examinations were not remarkable. Reflexes were hyperactive and a fine tremor of fingers was present.

Laboratory examinations showed a normal blood cell picture. The leukocyte count remained between 6300 and 12,000. Urine examinations were normal.

Other studies were: venous pressure 80 mm. of saline, circulation time (arm to carotid sinus) 14 seconds, x-ray of chest—the heart was within normal limits, lungs were clear except for small calcified area probably in the pleura, electrocardiogram—record suggested left sided enlargement and "strain."

Exophthalmometer measurements were 15 and 16 mm. in the right and left eyes before treatment and 16 and 17 mm. after treatment.

The patient's course is shown in Fig. 52. The temperature elevations were thought to be due to pharyngitis and tonsillitis. Throat cultures showed beta hemolytic streptococci and there was some white exudate on the tonsils. This cleared up with sulfadiazine throat spray. The patient became much less jittery with treatment. No change was noted in the thyroid gland.

At operation the gland was diffusely enlarged. Hemorrhage encountered was marked but not extreme. The postoperative course of the patient was uneventful. She complained of some hoarseness and discomfort at the site of operation. A small amount of bloody fluid was aspirated from the wound.

Pathological study of the removed tissue showed marked hyperplasia, with many areas of infolding of tall columnar epithelium with almost no colloid in the acini. The weight of the tissue removed was 33 gm.

#### Case V. Thiouracil Treatment after Demonstrated Failure to Respond to Iodine, with Febrile Reaction

H. D., a 47 year old colored woman, was admitted with the chief complaints of "jittery feeling," lump in neck and weight loss for six months.

Past history revealed that she had a large goiter removed twenty years ago at another hospital. She apparently had no symptoms of hyperthyroidism at that time. She was asymptomatic until the present episode.

The present illness began six months before admission with feeling of weakness and tiredness. For the last month she had been very nervous. Appetite remained good, but she lost 20 pounds in six months. She noticed a swelling in the neck. Four months ago her physician gave her Lugol's solution, ten drops three times a day for two weeks with some relief but she has had no treatment since.

The patient was first seen in the medical dispensary where a diagnosis of hyperthyroidism with a nodular goiter was made. She was admitted to the surgical service and placed on iodine therapy for two weeks (Fig. 53). Because of complete lack of improvement symptomatically and physically she was transferred to the medical service for thiouracil preparation.

Physical examination showed a temperature of 98.7 F., pulse 90 and blood pressure 136/80. The patient squirmed and fidgeted about the bed. The skin was loose, moist and warm. The eyes did not appear prominent and the lid slits were not wide, but there was some edema of the lids. The neck showed an old operative scar. The thyroid gland was diffusely enlarged on the right side, but slightly nodular. The left side showed a nodule the size of a small egg. The lungs were clear. The heart was enlarged to the left, the point of maximum

impulse being 8 cm to the left in the fifth interspace. There were systolic murmurs at the apex and pulmonic areas. Abdominal, pelvic and rectal examinations revealed no significantly abnormal findings. A fine tremor of the hands and quite active reflexes were present.

Laboratory work showed a normal blood cell picture. Leukocytes remained between 6000 to 7200. The urine was normal.

Other studies were: venous pressure 140 mm of saline, total serum protein 7.7 gm per 100 cc, throat culture—normal throat flora, urine culture—sterile,

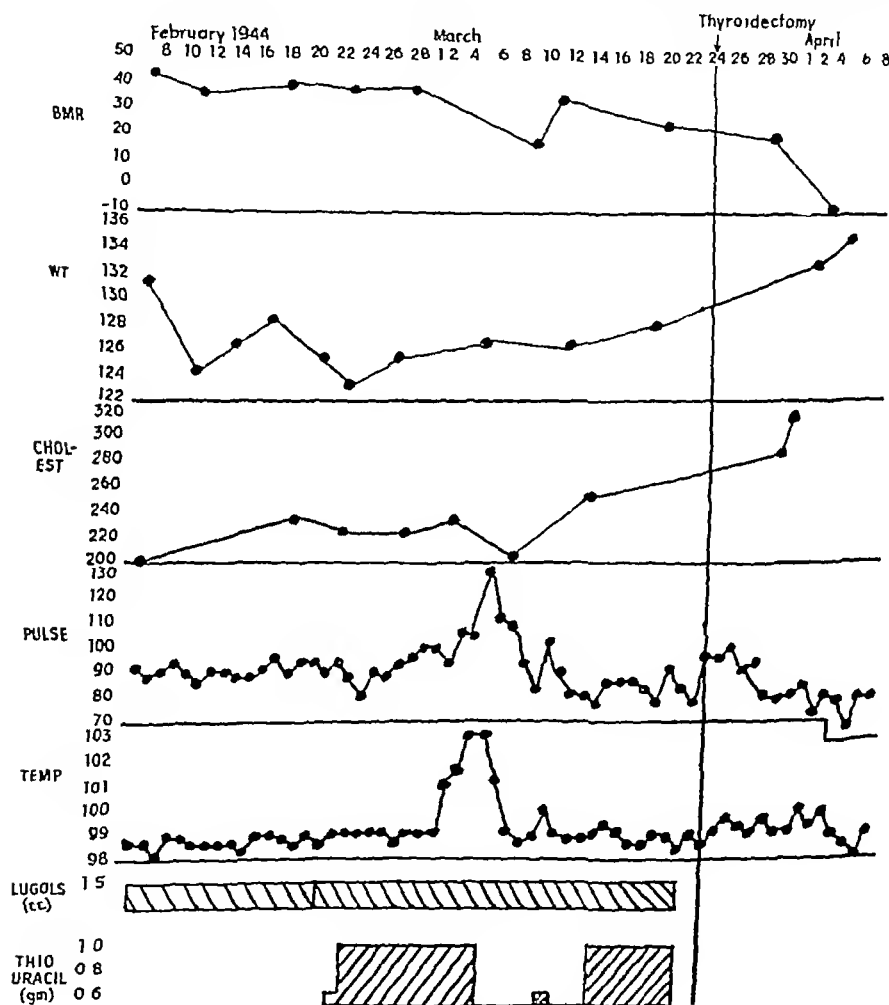


Fig. 53—Clinical course in Case V

blood culture at the time of fever—no growth, electrocardiogram—normal record except for tachycardia, x-ray of chest—lungs clear, heart enlarged, no evidence of substernal thyroid.

Exophthalmometer measurement in the course of treatment was 21 mm in both eyes.

The patient's course is illustrated by the chart. It was complicated by the development of fever which subsided on discontinuing thiouracil and recurred slightly on giving a small dose. Thiouracil was resumed again after three days.

and no fever was encountered. Although the basal metabolic rate had fallen from the previous level of plus 40 per cent to only plus 25 per cent, because of the patient's general symptomatic improvement and beginning weight gain and rise in cholesterol with a lowering of the pulse and blood pressure (to 100/66) she was considered by both surgeons and physicians to be in adequate condition for operation.

At operation there was much scarring from previous operation. The gland showed the gross characteristics of hyperplasia. With some difficulty many bleeding points were controlled and the wound was finally dry. The patient withstood the operation well.

The postoperative course was entirely uneventful. There was hoarseness for two days but the voice was normal at the time of discharge. Convalescence was carried out on the medical wards with improvement in nervousness and rapid weight gain.

Pathological examination of the removed tissue showed fetal and Hurthle cell adenomas. The adenomatous areas had small acini with little colloid and marked hyperplasia. The surrounding thyroid tissue showed marked hyperplasia with marked variation in the size of the acini and the amount of colloid in them. The weight of the removed tissue was 57 gm.

#### Case VI Simultaneous Thiouracil and Iodine Preparation in a Male Patient with Exophthalmos

J. D., a 35 year old white man was admitted with the chief complaint of nervousness of ten months' duration.

The present illness began with weight loss and craving for carbohydrate food. For five months the patient noted nervousness and for two months had palpitation at rest or on slight exertion. A few weeks ago friends commented on prominence of his eyes. Strength remained good. He lost 50 pounds in the course of the year. He had not received any medication.

Physical examination showed a temperature of 100.6 F., pulse 120 and blood pressure 160/70. The general appearance was of a thin, nervous person who talked rapidly and fidgeted with his hands. The eyes were very prominent. The sclerae were visible below the cornea but not above. There was mild diffuse injection of the conjunctivae. The lids were normal and the tension normal to digital pressure. Exophthalmometer readings: right eye 23 mm., left eye 22 mm. Tonsils were huge and injected. The thyroid gland was diffusely enlarged, soft with a slight bruit over entire region. The heart size was normal to percussion with a late systolic whistling murmur at apex. The lungs were clear. Abdominal, genital and rectal examinations were normal. There was a marked tremor of the hands.

Laboratory examinations showed a normal blood cell picture. Leukocyte counts remained between 7600 and 10000. Urine was normal except for 2 plus sugar on one occasion.

Other studies were: x ray of the chest—heart and aorta normal, lungs clear; no substernal thyroid; fasting blood sugar 93 mg. per 100 cc., electrocardiogram—high P waves and tachycardia; total serum protein 6.0 gm. per 100 cc., throat culture—normal throat flora.

The patient's course is illustrated by the chart (Fig. 54). He became less nervous and felt much stronger. He frequently complained of soreness and tenderness in both nipples which off and on had tender nodules in the areolar area and were slightly swollen. The patient's exophthalmos caused some concern since with treatment the right eye seemed to become more prominent. Exophthalmometer measurements remained at 22 mm. in the left eye but increased from 22 to 25 mm. in the right eye. Examination by Dr. Frank B. Walsh showed slight fullness of the lids and possibly low grade edema of the conjunctiva. The

eyes were easily pushed back into the orbits. It was Dr. Walsh's opinion that the patient presented only minimal signs which might suggest that he would develop progressive exophthalmos. The patient was followed closely in regard to his eyes because of the relatively much higher frequency of progressive exophthalmos in males than females with hyperthyroidism.

Subtotal thyroidectomy was carried out. The gland was quite firm and no technical difficulty was encountered. The postoperative course was complicated

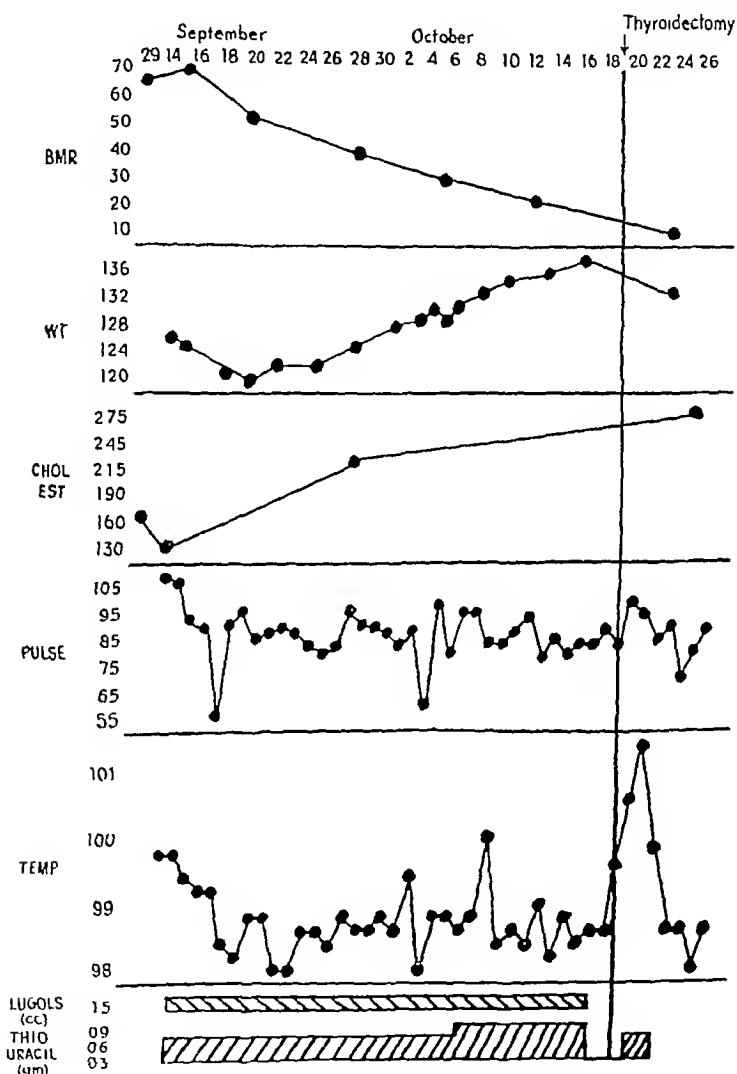


Fig 54—Clinical course in Case VI

by a marked hoarseness and cough with temperature elevation to 101.0° F for two days. This was thought to be due to laryngitis and tracheitis. The vocal cords were slightly thickened. The chest plate showed the lungs clear. Sulfamerazine was given for a few days and the symptoms and fever subsided. The remainder of the convalescence was uneventful.

Pathological examination of the tissue removed at operation showed generally slight to moderate hyperplasia. In some small foci there was marked hyperplasia.

Most of the acini were fairly large and filled with colloid. The removed tissue weighed 71 gm.

## BIBLIOGRAPHY

- 1 Fitz, R. J.A.M.A., 125:943 1944
- 2 Editorial J.A.M.A., 125 Sept 6, 1944
- 3 Editorial J Clinical End., 3(9) 526, 1944
- 4 Kennedy, T. H., Purves, H. D. and Griesbach W. L. Brit. J. Expt. Pathology 22:241 1941
- 5 Kennedy, T. H. Nature, London 150:233-234 1942
- 6 Richter C. P. and Clisby, K. H., Proc. Soc. Exper. Biol. & Med., 48:684 1941
- 7 Mackenzie, C. G. and Mackenzie, J. B. Endocrinology 32:185 1943
- 8 Astwood, E. B., Sullivan, J., Bissell A. and Tyslowitz, R. Endocrinology 52:210, No 2 (Feb) 1943
- 9 Astwood E. B. J. Pharm. & Exper. Therapeutics 78:79 (May) 1943
- 10 Purves, H. D. Brit. J. Exper. Path., 24:171 1943
- 11 Mackenzie, J. B. Bull. Johns Hopkins Hosp., 74:85 1944
- 12 Griesbach W. E. and Purves, H. D. Brit. J. Exper. Path., 24:174 1943
- 13 Griesbach, W. E. et al. Brit. J. Exper. Path., 24:185 1943
- 14 Mackenzie, C. G. Science, 94:518 1941
- 15 Whitehead, V. I. E. Brit. J. Exper. Path., 24(5) 192 (Oct) 1943
- 16 Chesney, A. M. Bull. Johns Hopkins Hosp., 43:261 1938
- 17 Rawson, R. W., Hertz, S. and Means, J. H. Ann. Int. Med., 19:829, 1943
- 18 Lowenstein et al. J. Clin. Endocrinol., June, 1944
- 19 Hughes, A. M. Endocrinology 34:69 1944
- 20 Bauman, E. J., Metzger N. and Marine D. Endocrinology 34:44 1944
- 21 Schachner H., Franklin, A. L. and Chaikoff I. L. Endocrinology 34:159 1944
- 22 Franklin, A. L. and Chaikoff I. L. J. Biol. Chem., 153:151 1944
- 23 Franklin, A. L. and Chaikoff I. L. J. Biol. Chem., 152:295 1944
- 24 Keston A. S. et al. J. Biol. Chem., 152:241 1944
- 25 Rawson R. W., Taunheimer J. F. and Peacock W., Endocrinology 34:245 1944
- 26 Franklin, A. L., Lerner S. R. and Chaikoff I. L. Endocrinology 34:265 1944
- 27 Dempsey E. W. Endocrinology 34(1) 27 1944
- 28 Rawson, R. W., Graham R. and Riddell, C. B. Ann. Int. Med., 19:405 1943
- 29 Astwood E. B. and Bissell A., Endocrinology 34:282, 1944
- 30 Jandorf B. J. and Williams, R. H. Am. J. Physiol., 141:91 1944
- 31 Means, J. H. and Lerman, J. Ann. Int. Med., 12:811 1938
- 32 Williams, R. H., Weinglass, A. R. and Kay G. A. Am. J. Med. Sciences, 207(6) 701 1944
- 33 Williams R. H., Weinglass, R. H. and Bissell, G. W. Endocrinology 34:317 1944
- 34 Meyer A. E., Collens, M. B. and Marine, D. Proc. Soc. Exper. Biol. & Med., 55:221 1944
- 35 Personal communication Dr. Stanton M. Hardy, Lederle Laboratories, Pearl River, New York
- 36 Astwood E. B. J.A.M.A., 122:78 1943
- 37 Astwood L. B., J. Clin. Endocrinol., 4(6) 229 1944
- 38 Williams, R. H. and Bissell, G. W. New England J. Med., 229:397 1943
- 39 Williams, R. H. M. Clin. North America, 28(5) 1043 1944
- 40 Williams, R. H. Science, August 13 1943 p. 156
- 41 Williams, R. H. New England J. Med., June, 1944 p. 657
- 42 Rawson R. W., Evans, R. D., Means, J. H., Peacock, W. C., Cortell R. E. and Lerman, J. J. Endocrinol., 4:1 1944
- 43 Haler D. Brit. Med. J., 1:387 1944



- 44 Kahn, J and Stock, R B J.A.M.A., 126(6) 358, 1944
- 45 Martin, E M Canad M A J, 51 39 (July) 1944
- 46 McGregor, J K Canad M A J, 51 37 (July) 1944
- 47 Watson, E. M and Wilcox, L D Canad M A J, 51 29 (July) 1944
- 48 Williams, R W *et al* J Clin Endocrinol., 4 58, 1944
- 49 Bartels, E C J.A.M.A., 125(1) 24, 1944
- 50 Gabrilove, J L and Kert, J M J.A.M.A., 124 504, 1944
- 51 Paschkis, K E, Cantarow, A, Rokoff, Walding and Tourish J Clin Endocrinol., 4 179, 1944
- 52 McGavach, T H, Gerl, A J, Vogel, M and Schwimmer, D J Clin Endocrinol., 4 249, 1944
- 53 Reveno, W S J.A.M.A., 126(3) 153, 1944
- 54 Mayer, W B Bull Charlotte Mem Hosp, 1 31, 1944
- 55 Palmer, V Bull Sch Med Univ Md., 28 125, 1944
- 56 Newman, E V., Reinhoff, W F and Rich, A R Bull Johns Hopkins Hosp., 74 153, 1944
- 57 Spicer, S S, Daft, F S., Sebrell, W H and Ashburn, L I U S Public Health Reports, 57 1559 (Oct 16) 1942
- 58 Goldsmith, E. D., Gordon, A S, Finkelstein, G and Charipper, H A J.A.M.A., 125 847, 1944
- 59 Mulvany, J H Amer J Ophth, 27(6, 7, 8) 1944
- 60 Salter, W T and Toley, M H M CLIN NORTH AMERICA, March, 1944, p 484
- 61 Brain, W R and Turnbull, H M Quart J Med, 7 293, 1938
- 62 Means, J H Ann Int Med., 19 567, 1943

## MEDICAL MYCOLOGY

EDMUND L. KEENEY, M D \*

It is the purpose of this clinic to discuss the common fungous diseases and point out some of the significant and the recent contributions made for each disease. For the sake of clarity and of convenience the various superficial mycotic infections will be discussed together under the heading of "dermatophytosis" and the deep-seated mycotic infections will be taken up individually.

### DERMATOPHYTOSIS

Dermatophytosis is a more or less superficial infection of the skin, the hair and the nails caused by any one of the fungi known as the dermatophytes. The fungi included in the genera of *Trichophyton*, *Epidermophyton*, *Microsporum* and *Candida* (*Monilia*) are referred to as the dermatophytes. These parasites may infect many different body regions and have a wide range of morbid anatomical expressions. It is because of these two latter characteristics that so many confusing terms have invaded the literature. *Tinea*, which means "worm," precedes *pedis*, *capitis*, and *cruris* on occasions to denote the region of the body infected and then on other occasions is used before *circinata* and *imbricata*, to describe an anatomical expression of the infection.

Only one or two species of each of the genera referred to above are of clinical importance. *Trichophyton mentagraphytes* and *Trichophyton rubrum* commonly infect the skin and the nails of the feet, *Epidermophyton floccosum* commonly infects the skin of the groin, *Microsporum audouini* and *Microsporum felineum* commonly infect the hairs of the scalp in children, and *Candida albicans*, which may also produce deep-seated lesions, commonly infects the mucous membranes of the mouth (thrush) and the vagina.

**Diagnosis.—Clinical Picture**—The matter of making a clinical diagnosis of dermatophytosis is usually not difficult. Occasionally, however, chemical dermatitis and skin manifestations of hypersensitivity simulate dermatophytosis. Therefore, because the diagnosis of fungous infection cannot be made with certainty in all cases on clinical grounds alone, the laboratory evidence of the presence of a dermatophyte by

---

From the Medical Clinic, the School of Medicine, Johns Hopkins University and Hospital, Baltimore, Maryland. Part of the work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the Johns Hopkins University.

\* Instructor in Medicine, Johns Hopkins University School of Medicine; Assistant Visiting Physician, Johns Hopkins Hospital.

microscopic examination or by culture is essential in a scientific study of a skin affection where dermatophytosis is suspected

The dermatophytes produce a characteristic sporulating mycelium in culture (Fig 55) but they are present in the skin and the hair

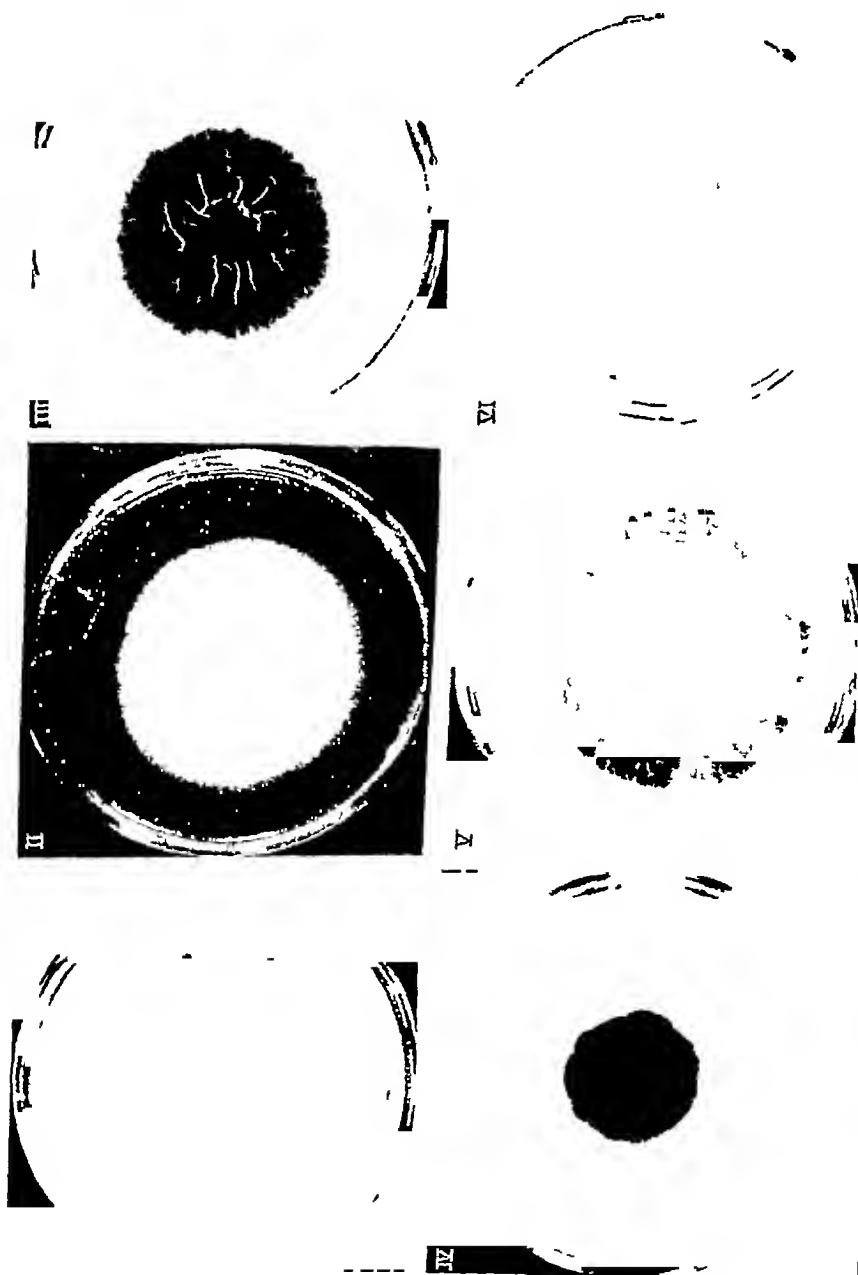


Fig 55 - The dermatophytes I, *Trichophyton mentagrophytes* II, *Trichophyton rubrum* III, *Epidermophyton floccosum* IV, *Candida albicans* V *Microsporum audouinii* VI, *Microsporum felinum*

as continuous or fragmented hyphae. The demonstration of hyphae, by microscopic examination of material from the infected areas, is sufficient to make a diagnosis of dermatophytosis.

**Laboratory Examination**—The material to be studied must be collected properly. A scalpel should be used to obtain scrapings of skin from lesions on the toes and in the groin. The active edge, not the center, of the lesion should be scraped. It must be remembered that fungous infections heal from the center and if the hyphae are to be found they will be located at the periphery of the lesion. If the lesion is vesicular, the roof of the vesicle should be completely removed with scissors and if the hair is affected an affected hair should be epilated with forceps. The specimen for examination should then be placed upon a slide and covered with 10 per cent sodium hydroxide. Several hours must elapse to allow the sodium hydroxide to clear the specimen before making the microscopic examination.

It is also desirable to culture material from infected areas. Skin scrapings, or the roof of a vesicle or an infected hair should be planted on Sabouraud's dextrose agar and incubated at 30° C. The identification of the fungus by its gross and microscopic cultural characteristics should be attempted only by an experienced mycologist. The isolation and classification of the fungus is an academic nicety and is not essential for the proper treatment of the patient.

**Skin Test**—It is important to discuss briefly the value of the skin test in diagnosing dermatophytosis. Once the body has become infected by a fungus certain alterations occur which affect the reactivity of the tissues toward subsequent contact with the fungus or the protein of the fungus. This altered reactivity that results from infection is spoken of as "bacterial hypersensitivity," "hypersensitivity of infection," or "tuberculin type hypersensitivity." It is quite possible that an "anaphylactic" type of hypersensitivity to the polysaccharide fraction of the fungus also develops.

There is available on the commercial market a crude extract of the *Trichophyton* species which is suitable for the testing of "hypersensitivity of infection." This extract is known as *trichophytin*. The test is performed by injecting 0.1 cc. of a 1:30 dilution of trichophytin (Lederle) intradermally on the volar surface of the forearm. The test is interpreted forty-eight hours later and if an area of erythema and induration occurs at the site of injection, it is spoken of as being positive. The positive test only indicates that at some time in the immediate or distant past the host has been infected with fungi and is therefore of limited value in making a diagnosis of dermatophytosis. A negative trichophytin test is helpful in ruling out dermatophytosis just as a negative tuberculin test is of assistance in ruling out a tuberculous infection.

**Fluorescence Test**—The fact that hairs infected by the *Microsporum* dermatophytes fluoresce under filtered ultraviolet radiation is frequently used as an aid in the diagnosis of fungous infection of the scalp in children. Inexpensive units for the production of filtered ultraviolet radiation are available on the commercial market. These units are

commonly referred to as "Wood's lights," being named for their inventor, Dr Robert Wood, Emeritus Professor of Physics at the Johns Hopkins University

**Treatment**—A compound to be effective in the treatment of dermatophytosis must first possess the power to inhibit the growth of fungi or actually kill the fungi. Secondly, it must be able to penetrate the stratum corneum and come into contact with the fragments of hyphae that are embedded there. Penetration can be abetted by incorporating the compound into vehicles that possess the power of penetration in their own right. Thirdly, the compound should possess an antibacterial effect, because essentially every fungous infection is complicated by secondary bacterial infection and the hypersensitive reaction to this bacterial infection. Fourthly, the compound and the vehicle in which it is placed should be neither irritating nor sensitizing.

As a result of research recently conducted under the auspices of the Office of Scientific Research and Development<sup>1, 2, 3, 4</sup> there have been developed two preparations which satisfy the above qualifications. These are *propionate-propionic acid ointment*\* and *undecylenate-undecylenic acid ointment*†. There is little difference in the clinical effectiveness of these two ointments, but the propionate-propionic acid ointment possesses more antibacterial effect in vitro than the undecylenate-undecylenic acid ointment. It is of further importance to point out that by in vitro tests the propionate-propionic acid ointment has more fungistatic activity than full strength Whitfield's ointment and 10 per cent ammoniated mercury ointment and has more antibacterial effect than full strength Whitfield's ointment, 10 per cent ammoniated mercury ointment, 5 per cent sulfathiazole ointment and 0.5 per cent tyrothricin ointment.

The propionate-propionic acid ointment and the undecylenate-undecylenic acid ointment are satisfactory for the treatment of dermatophytosis of the feet, the groin and the smooth skin and either preparation is an improvement over any one method of treatment that has been formerly employed. In this respect the treatment of dermatophytosis has been fairly standardized.

For the treatment of dermatophytosis of the feet, either ointment should be applied over the toes, between the toes and under the toes every night. The following morning the ointment should be removed with soap and water or with a towel and the feet dusted with talcum. A calcium propionate dusting powder‡ is now available which is superior to pure talcum powder. Some of the powder should also be

\* Propionate-propionic acid ointment: sodium propionate 16.4, propionic acid 3.6, propylene glycol 5.0, n-propyl alcohol 10.0, "carbowax (4000)" 35.0, zinc stearate 5.0, water sufficient to make 100.0.

† Undecylenate-undecylenic acid ointment: undecylenic acid 10.0, triethanolamine 6.0, propylene glycol 14.0, "carbowax (1500)" 10.0, "carbowax (4000)" 40.0, water sufficient to make 100.0.

‡ Calcium propionate dusting powder: calcium propionate 15.0, talcum 85.0.

dusted into the shoes. This treatment must be adhered to until the lesions have completely healed and then continued for several weeks thereafter. It is important to stress that the use of keratolytic agents, the procedure of opening widely vesicular lesions on the soles of the feet, and the use of warm potassium permanganate (1:3000) soaks for acute eczematoid lesions should not be lost sight of and must supplement the use of either the propionate-propionic acid ointment or the undecylenate-undecylenic acid ointment.

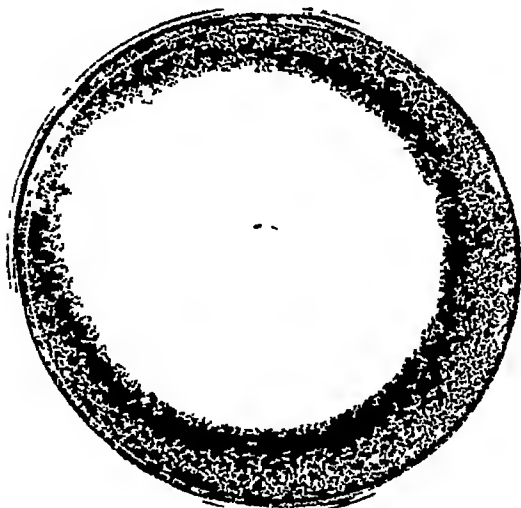


Fig. 56.—Demonstrating the fungistatic effect of 10 per cent sodium caprylate jelly on *Candida albicans* (Agar cup-plate technic of Ruehle and Brewer). The clear area surrounding the cup represents the zone of complete inhibition.

For the treatment of dermatophytosis of the groin or smooth skin, either ointment should be applied every night and every morning. The ointment should also be applied to the normal skin immediately surrounding the infected area. The treatment must be continued for approximately one week after the lesions have completely healed.

To date the only satisfactory method of treating dermatophytosis of the hairs of the scalp has been *x-ray epilation*. This treatment must be administered by an expert. At the moment there are severe epi-

demics of dermatophytosis of the scalp in New York City, Pittsburgh, Philadelphia and Hagerstown, Maryland Under the auspices of the United States Public Health Service extensive research is being conducted in these communities and it is to be hoped that a satisfactory scheme of medical treatment will be developed as a result of these investigations

The development of the *fatty acids* as inhibitors of pathogenic fungi promises to lend assistance in the treatment of infections due to *Candida albicans* in the mouth (thrush) and in the vagina A 20 per cent solution of sodium caprylate adjusted to pH 7.4 and applied three or four times daily to lesions in the mouth has been very effective A 10 per cent sodium caprylate jelly has been found to be very active in vitro against *Candida albicans* (Fig. 56) and its use in vivo in the treatment of vaginal infections due to this organism appears to be promising

### SPOROTRICHOSIS

Sporotrichosis was first discovered in Baltimore by Schenck<sup>5</sup> in 1896 Four years later Hektoen and Perkins<sup>6</sup> named the causative fungus, *Sporotrichum schenckii* The great majority of the reported cases have occurred in France, the United States and South America

It is believed that the fungus grows on vegetation and that humans are infected from this source Many cases have followed wounds of the upper extremity by barberry thorns, by straw and by grains Accidental laboratory infections have occurred and there is on record a case in which there was direct transmission from human to human.

**Diagnosis—Clinical Picture**—The clinical picture of a typical case is so striking that, once seen, the disease will always be readily recognized Extending from the primary lesion, which is usually an ulcer or abscess about the wrist, there will be seen upon the surface of the extremity a line of hard or soft elevated nodules that are neither hot nor tender Between these nodules there are usually reddened lines that demarcate the course of the lymphatic vessels If sufficient time has elapsed between the onset of the disease and the time when the patient first presents himself for treatment, some of the softer nodules will have developed a draining sinus from which pus can be expressed It is rare for the disease to spread beyond the regional lymph glands but Beurmann<sup>7</sup> of France, has reported cases in which metastatic lesions have occurred in the lungs, the liver and the testicles It is not uncommon to discover that the patient with sporotrichosis is suffering from some debilitating disease which lowers his resistance to infection sufficiently to allow the fungus to gain a foothold One of our cases has diabetes mellitus and there are many cases reported in the literature in which pulmonary tuberculosis has preceded the infection by *Sporotrichum schenckii*

**Laboratory Examination**—The diagnosis is established by culturing the organism from a subcutaneous abscess A higher percentage of

positive cultures will be obtained if the material to be cultured is aspirated from an abscess that has not as yet opened. It is difficult to identify the organism microscopically from smears of pus.

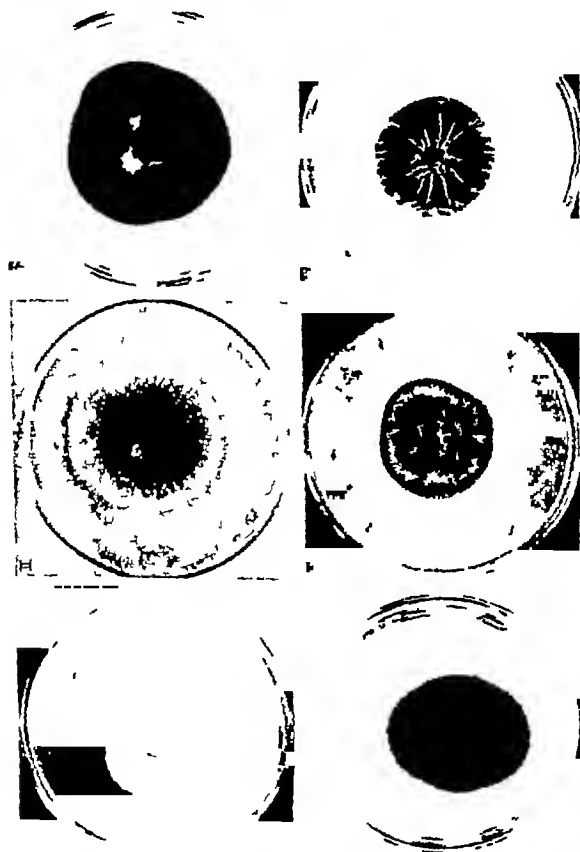


Fig. 37—Fungi that produce deep-seated infections. I, *Cryptococcus neoformans*. II, *Sporotrichum schenckii*. III, *Blastomyces dermatitidis*. IV, *Coccidioides immitis*. V, *Phialophora verrucosa*. VI, *Histoplasma capsulatum*.

The character of the growth of *Sporotrichum schenckii* on Sabouraud's dextrose agar is distinctive. At first the colony is whitish, shiny and moist, resembling a bacterial growth. As the age of the culture



increases the whitish color changes to a light tan, then to a coffee brown and finally may become black. The surface of the colony usually remains shiny but becomes wrinkled with age (Fig 57)

*Skin Tests*—The diagnosis can further be established by skin testing. Moore and Davis<sup>8</sup> as early as 1918 obtained positive "tuberculin-like" skin tests by injecting intradermally a killed spore suspension. We have recently been able to demonstrate positive skin reactions with 0.1 cc of a 1:1000 dilution of a two weeks old broth filtrate of *Sporotrichum schenckii* (Fig 58). The broth filtrate gives negative reactions in normal controls.

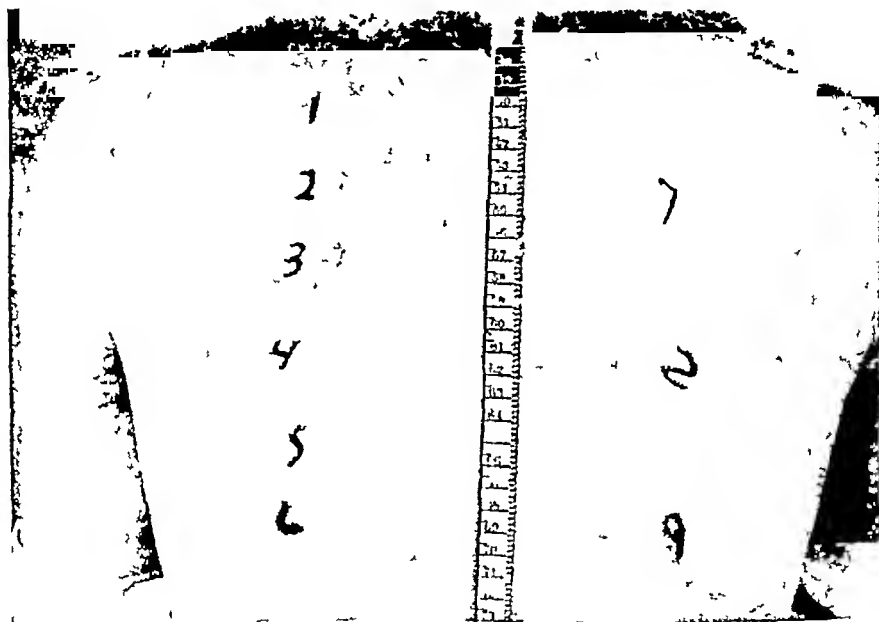


Fig 58—Demonstrating the results of skin tests with 1:1000 dilutions of broth filtrates of *Sporotrichum schenckii* prepared from stock and autogenous species. Numbers 1, 2, 3, 4, 5 and 6 represent results obtained from stock strain filtrates prepared after cultures had grown 1, 2, 3, 4, 5 and 6 weeks, respectively. Numbers 7, 8 and 9 represent results obtained from autogenous strain filtrates prepared after cultures had grown 2, 4 and 6 weeks, respectively. Sufficient antigen was obtained after a growth of 1 to 2 weeks to elicit positive skin reactions. Tests were read after 48 hours.

*Treatment*—The disease usually responds dramatically to the administration of *iodides*. Just recently we have treated two patients with parenteral injections of *fatty acids*. One patient received intramuscular injections and local applications of sodium undecylenate and the second patient received intravenous injections and local applications of sodium caprylate. Both fatty acid salts are effective in vitro against *Sporotrichum schenckii*.<sup>3</sup> Neither patient improved under intensive treatment but both patients responded readily to the oral administration of potassium iodide (Figs 59 and 60).



Fig 59—Illustrating the effectiveness of potassium iodide in the treatment of sporotrichosis. I and II, Before treatment. III and IV Eight weeks after treatment. Potassium iodide was administered to the point of intolerance which for this patient was 36 gm daily Patient was discharged taking 25 gm. daily

We have not been able to demonstrate by in vitro tests that the sulfonamides or penicillin are sufficiently effective to warrant their use clinically in the treatment of this fungous infection<sup>9, 10</sup>

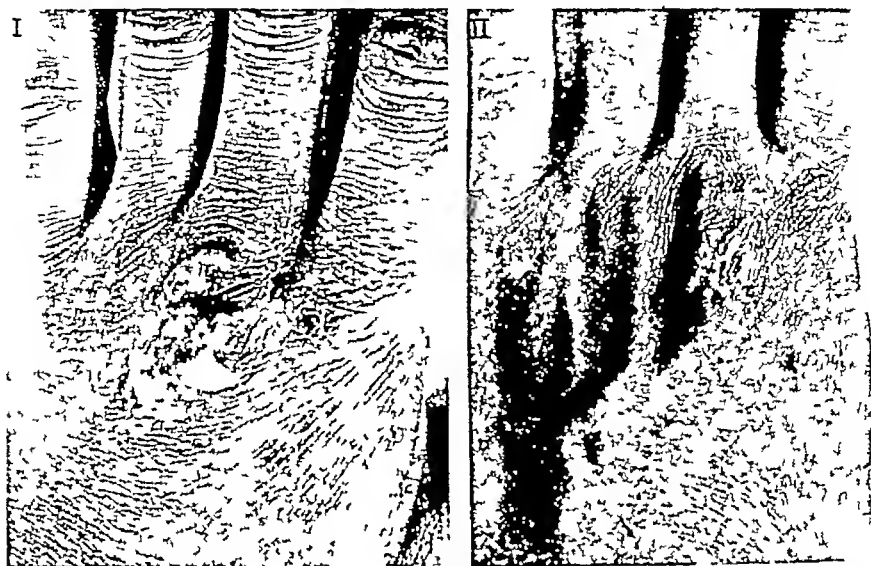


Fig 60—Illustrating the effectiveness of potassium iodide in the treatment of sporotrichosis I, Before treatment II, Four weeks after treatment Efficacious results were obtained with small doses of potassium iodide (6 gm daily)

### COCCIDIOIDOMYCOSIS

Coccidioidomycosis is the name originated by Dickson<sup>11 12</sup> of Stanford University for the disease produced by the fungus, *Coccidioides immitis*. The disease was actually first reported in South America in 1892 by Wernicke<sup>13</sup>. It is imperative not to confuse coccidiosis with coccidioidomycosis. Coccidiosis is an infection produced by one of the animal parasites included in the order Coccidia of the class Sporozoa. The Coccidia commonly infect the intestines of chickens and other birds, the livers of rabbits, and the intestines of dogs and cats.

The fungus, *Coccidioides immitis*, occurs in the soil of arid regions of the United States, that is, the San Joaquin Valley in Southern California, Southern Arizona, Southern Utah, Western Texas and a portion of New Mexico, and has also been found in Northern Mexico, Italy and Hawaii. Emmons<sup>14</sup> has recently suggested that the fungus may have a rodent reservoir.

**Diagnosis—Initial Infection**—Very frequently individuals living in endemic areas may become infected without manifesting any clinical evidence of the disease. Furthermore, the lesions heal and confer upon these individuals immunity against subsequent infection. Individuals moving into or through endemic areas may acquire an initial infection

which manifests itself by signs and symptoms characteristic of many acute respiratory infections. There is usually fever from  $99^{\circ}$  to  $101^{\circ}$  F accompanied by malaise, backache, chest pain, cough, headache, chills and night-sweats. The onset of these symptoms may be either abrupt or insidious. A diagnosis of "influenza" is frequently made.

Approximately two weeks after the onset of the initial infection, symptoms and signs of hypersensitivity may occur. About 5 per cent of the patients develop either erythema nodosum or erythema multiforme and a small per cent complain of pains in the joints.

The pulmonary lesions, which roentgenologically resemble tuberculous infiltrations, usually undergo fibrosis and calcify. Occasionally necrosis within the pulmonary lesions will cause the development of a cavity. The cavity usually closes spontaneously, is thin-walled and may be confused with a tuberculous cavity. Interestingly enough the cavity may persist and remain "silent" except for the presence of coccidioides in the sputum and an occasional hemoptysis which appears after exertion. Otherwise the patient is well and resists exogenous and endogenous reinfection.

**Progressive Disseminated Infection.**—The fungus disseminates in only about 0.1 per cent of the patients infected, but when it does the result is fatal. The symptomatology of the progressive disseminated infection depends entirely on the sites to which the fungus has spread. In white patients meningitis is common and the chronic course simulates tuberculous meningitis. Furthermore, tuberculous spread to the lymph nodes and skin. In the dark skinned races there is more of a tendency to the development of multiple subcutaneous and joint abscesses. The ankle joint particularly for some reason is frequently singled out.

The term "coccidioidal granuloma" which is commonly used in the literature to describe the progressive disseminated type of infection is an unfortunate one and should be abandoned. Actually the residual lesions of the initial infection as well as the lesions of the progressive disseminated infection are known to be granulomatous in their histologic structure. It is better, therefore, to speak of 'initial' and 'disseminated' coccidioidomycosis for these terms connote the pathogenesis of the disease.

**Laboratory Diagnosis.**—*Coccidioides immitis* exhibits marked dimorphism. It grows on agar as a white cottony mold which pigments with age (Fig. 57). Old cultures contain myriads of very large, thick-walled spores known as chlamydospores. These spores which are particularly adapted for maintaining vitality through long periods of dormancy are considered to be the infective form of the fungus occurring in nature. When these spores are injected into animals they become spherical and enlarged. These large spherical cells, commonly referred to as 'spherules' give rise to endospores by cleavage of their cytoplasm. The endospores escape when the wall of the spherule ruptures.

and repeat the parasitic phase of the life cycle. It is the "sphe" that is found in the sputum of patients infected with *Coccidi immitis*.

Patients who are infected or have been infected with *Coccidi immitis* give a positive "tuberculin-like" skin reaction to the dermal administration of 0.1 cc. of a 1:100 dilution of *coccidi*. Furthermore, coccidioidin can be employed as an antigen for precipitation and complement fixation tests. Precipitins are usually present in the initial infections that are clinically apparent but are absent in disseminated infections. The titer of complement fixation usually varies with the severity of the infection.

The sedimentation rate of red corpuscles is accelerated in *coccidioidomycosis*. There is an increase in the leukocyte count at the initial infection with a concomitant eosinophilia. As the infection is arrested a relative and absolute lymphocytosis occurs.

**Treatment**—There is no specific form of treatment for *coccidioidomycosis*. In vitro and in vivo tests with the sulfonamides have failed with failure. Penicillin likewise is ineffective. The use of thymoniodides have never given satisfactory results. A strict regimen of rest is the best method of effecting a cure. In other words, the patient should be treated as though he had tuberculosis and should remain in bed until he has clinically recovered, until the x-rays have indicated the lesions to be regressing and until the sedimentation rate has returned to normal.

### BLASTOMYCOSIS

This disease was first discovered in Baltimore in 1894 by Gilchrist, who later<sup>16</sup> named the causative fungus *Blastomyces dermatitidis*. Actually the name blastomycosis is doubly a misnomer. It was thought that the causative organism was a true yeast and since it was thought that "*Blastomyces*" was the proper scientific name for the yeasts. Actually, however, the organism is not a true yeast though it has a yeastlike form in the tissues, and *Saccharomyces* is the proper scientific name for yeasts and not "*Blastomyces*."

**Diagnosis—Clinical Picture**—In the majority of cases the primary lesion appears on the skin of the face, hands, wrists or forearms. There first appears a firm papule and about this a number of secondary nodules develop which gradually enlarge and coalesce. The lesions break down and discharge purulent material from their centers. As the lesion progresses there appears a large, elevated mass of tissue with an irregular ulcerated surface that resembles somewhat a tuberculous ulcer. Healing occurs first in the central portion of the lesion and is followed by the formation of scar tissue.

The disease tends to progress slowly. Dissemination may occur by spread through the subcutaneous tissues, by contact, and by way of the lymphatics or the blood stream. Any organ or tissue in the

may be attacked. The lungs are frequently involved and the symptoms and signs of pulmonary blastomycosis bear a striking resemblance to those of pulmonary tuberculosis.

**Laboratory Diagnosis**—The diagnosis is established by demonstrating the organism in pus or sputum. In the body tissues the fungus occurs only as a round or oval yeastlike cell which reproduces by budding. These cells are easier to demonstrate if the material to be examined is first treated with 20 per cent sodium hydroxide. The finding of doubly-contoured budding cells with granular contents and which in size are slightly smaller than leukocytes makes the diagnosis certain.

Cultures are readily obtained on Sabouraud's dextrose agar if there are not too many contaminating bacteria. The colonies first appear smooth and grayish but soon become wrinkled. Finally a white, cottony growth with a central umbo develops (Fig. 57). Cultures on blood dextrose agar incubated at 37° C. do not develop a filamentous growth but remain yeastlike in appearance.

**Skin Test**—The diagnosis can further be established by skin testing. A tuberculin-like skin reaction is obtained in patients with blastomycosis by injecting intradermally a heat-killed vaccine prepared from the yeastlike form of the fungus.

**Treatment**—If the patient presents himself in the early stages of the disease when the lesion is small and accessible, the *surgical removal* of the lesion is advisable. If, however, the lesion is not suitable for surgical excision *x-ray therapy* in addition to large doses of *potassium iodide* should be recommended.

If the disease has disseminated, iodides are usually ineffective and actually may be dangerous in patients who have developed a hypersensitivity to the fungous infection. Martin and Smith<sup>17, 18</sup> have properly recommended desensitization with a heat-killed vaccine before the institution of iodide therapy in patients who are hypersensitive. They believe that satisfactory results can be obtained often from iodide therapy in systemic blastomycosis if desensitization is first carried out.

Recently we have demonstrated<sup>9, 10</sup> by *in vitro* studies that the sulfonamides and penicillin are not effective against *Blastomyces dermatitidis* and we feel that their use in the treatment of cutaneous or disseminated blastomycosis is not indicated.

#### CRYPTOCOCCOSIS (TORULOSIS)

Cryptococcosis was first described in Germany in 1895 by Busse<sup>19</sup> and Buschke.<sup>20</sup> The causative fungus, *Cryptococcus neoformans* (*Torula histolytica*), is a yeastlike organism which has a special affinity for the tissues of the central nervous system but which may also attack the lungs as well as other organs of the body. It may also produce a localized infection of the skin.

**Diagnosis.—Clinical Picture**—As a rule the disease begins insidiously with symptoms pointing to involvement of the central nervous system.

Persistent severe headache, stiffness of the neck and vomiting are common complaints. Later dimness of vision and diplopia may occur. Convulsions are not uncommon. Examination of the spinal fluid usually reveals an increase in pressure with an increase in lymphocytic cells and occasionally there is an increase in the albumin and globulin content. A specific diagnosis cannot be made from these signs and symptoms, and it is not until the yeast cells are demonstrated in the spinal fluid sediment or the organism cultured on Sabouraud's dextrose agar that one can be certain of the diagnosis.

The lungs are frequently affected and the clinical picture is often confused with pulmonary tuberculosis and other pulmonary mycotic infections. The primary lesion is thought to occur in the lungs with metastases occurring to the brain by way of the blood stream. The organism may similarly disseminate to involve other organs of the body, particularly the spleen, liver, kidneys and skin.

*Laboratory Examination*—The diagnosis is established by demonstrating budding yeast cells in the centrifuged spinal fluid sediment. In a Gram's stain preparation these cells stain dark blue with a reddish capsule.

On Sabouraud's dextrose agar the organism grows slowly. At first the growth is moist, smooth and cream colored. As the culture ages the color changes to yellow and then to brown (Fig. 57).

*Treatment*—No effective method of specifically treating this fungous infection has been reported. The disease is slowly progressive and usually fatal. The administration of large doses of *potassium iodide* to the point of intolerance is warranted. The organism is not very susceptible to the *sulfonamides*, but sulfathiazole in a concentration of 10 per cent completely inhibits the growth *in vitro*<sup>9</sup> and because of the lack of specific methods of treatment an intensive course of sulfonamide therapy is justifiable. Penicillin does not inhibit the growth of the organism *in vitro*<sup>10</sup> and its use in the treatment of this disease is not indicated. The treatment for the most part must be purely symptomatic.

#### CHROMOBLASTOMYCOSIS

The first case of chromoblastomycosis was studied by Pedroso<sup>21</sup> in Brazil in 1911. Lane<sup>22</sup> described the first case in the United States in 1915 and Medlar<sup>23, 24</sup> in the same year was the first to grow the causative fungus, which was named *Phialophora verrucosa*. The disease, although rare, is worldwide in distribution. Eight cases have now been reported in the United States. It is important to note that many fungi have been described as causing chromoblastomycosis but most of the cases have been due to either *Phialophora verrucosa* or *Hormodendrum pedrosoi*. The name of the disease, chromoblastomycosis, was selected on the basis of the dark color of the fungous cells in the lesions. Then, too, the disease was thought to resemble in many ways blastomycosis. All races are susceptible. The laboring classes, particu-

larly the agriculturists, are almost exclusively affected. This is probably due to their contact with vegetation.

**Diagnosis.**—The disease is confined to the skin and for the most part the lesions are unilateral and occur on the lower extremities. There is frequently a striking similarity to blastomycosis. The typical lesions which develop over a period of several years are pedunculated cauliflower-like excrescences which occasionally ulcerate. Elephantiasis may develop concomitantly. Regional adenopathy frequently occurs and is thought to be the result of secondary bacterial infection in the primary mycotic lesion. Systemic manifestations to the infection do not occur unless there is a secondary bacterial infection. Local pain and pruritus infrequently occur.

The diagnosis is established by demonstrating brownish, thick-walled, septate cells in the pus removed from fresh lesions. In the old necrotic lesions small septate filaments may be observed.

The organism grows very slowly on Sabouraud's dextrose agar. The colonies appear velvety and vary in color from dark olive to black (Fig. 57).

**Treatment.**—The disease is slowly progressive but never fatal. If the patient is seen early in the course of the disease the lesion or lesions should be excised. If the disease has progressed so that surgical removal is impossible, x-ray therapy combined with large doses of potassium iodide should be recommended. We have recently demonstrated<sup>9</sup> that *Phialophora verrucosa* is completely inhibited in vitro by sodium sulfamerazine in a concentration of 50 mg. per cent. Therefore, the use of sodium sulfamerazine or sulfamerazine in the treatment of chromoblastomycosis due to *Phialophora verrucosa* is warranted. Penicillin does not inhibit the growth of *Phialophora verrucosa* in vitro<sup>10</sup> and its use in the treatment of this disease is not indicated.

#### HISTOPLASMOSIS

The disease, histoplasmosis, was first discovered in the Panama Canal Zone by Darling<sup>23</sup> in 1906. Darling originally believed the causative organism was a protozoan and therefore gave it the name *Histoplasma capsulatum* and accordingly named the disease histoplasmosis. De Monbreum<sup>26</sup> in 1934 reported that the organism could be grown in yeast-like and mycelial forms. Furthermore, De Monbreum<sup>27</sup> produced the disease in monkeys and demonstrated that the intracellular phase of the parasite was the yeastlike form. He firmly established the fungus as the etiologic organism in histoplasmosis. As a result of his studies, De Monbreum proposed to change the name of the fungus and of the disease because of Darling's misconception of the systemic position of the organism but since Darling created a new generic and a new specific name for the parasite such a change is not warranted. The disease is not common and to my knowledge the diagnosis has been made before autopsy in only one reported case.



**Diagnosis—Clinical Picture**—The picture is usually that of emaciation, weakness, fever, anemia, leukopenia and splenomegaly. Hepatomegaly, ulcerative colitis and lymphadenopathy have been described. Various skin manifestations such as erythema, purpura and urticaria have been observed. It is advisable to consider histoplasmosis in the differential diagnosis of any obscure case of splenomegaly, particularly if the splenomegaly is associated with fever and leukopenia. Furthermore, it is important to examine the stools for fungi in patients with refractive diarrhea and ulcerative colitis, especially if no pathogenic organisms have been isolated.

**Laboratory Examination**—The fungus in its parasitic phase is a small yeastlike organism ranging in diameter from 2 to 3 microns. These yeastlike bodies resemble closely the Leishman-Donovan bodies of kala-azar and invade the mononuclear cells in enormous numbers. In cases in which the diagnosis of histoplasmosis is suspected the mononuclear cells in the circulating blood and in the bone marrow should be examined carefully under an oil immersion lens for intracellular bodies. If there is enlargement of the lymph glands, a biopsy should be made.

Cultures should be made on Sabouraud's dextrose agar and blood dextrose agar from the blood and the sternal bone marrow. If there is enlargement of the lymph glands a portion of the gland removed for biopsy should be pulverized and cultured. On Sabouraud's dextrose agar the organism produces a white, cottony growth (Fig 57). Spores ranging in size from 10 to 25 microns are produced and from these spores rise finger-like projections, 5 microns in length. The growth on blood dextrose agar is yeastlike.

**Treatment**—Because the diagnosis of histoplasmosis is rarely made before death, treatment for this fungous infection has not been developed. We have recently demonstrated<sup>9</sup> by *in vitro* experiments that the growth of *Histoplasma capsulatum* is completely inhibited by *sodium sulfathiazole* in a concentration of 50 mg per cent. Therefore the possible clinical effectiveness of sodium sulfathiazole or sulfathiazole in the treatment of histoplasmosis might be anticipated. Penicillin<sup>10</sup> does not inhibit the growth of *Histoplasma capsulatum* *in vitro* in concentrations that would warrant its use clinically.

### ACTINOMYCOSIS

The term actinomycosis does not refer to one specific disease caused by one specific organism. The term does indicate an infection due to an actinomycete. In man there are three well defined types of infection caused by species of actinomycetes. (1) The most common type is caused by *Actinomyces bovis*. This organism is an anaerobic, nonacid-fast, gram-positive actinomycete that is responsible for the cervicofacial, thoracic and abdominal lesions that are so well known to all clinicians. It is also the cause of lumpy jaw in cattle. (2) Another type of infection is caused by *Nocardia asteroides*, an aerobic, acid-fast

staining organism that is frequently the cause of pulmonary and brain lesions (3) The third type of infection is caused by *Actinomyces madurae*. This organism is the etiologic agent in Madura foot, a disease which is endemic in India, particularly in the city of Madura This discussion will be limited to infections produced by *Actinomyces bovis* and *Nocardia asteroides*

**Actinomycosis Due to *Actinomyces Bovis***—The mode of infection and transmission has not been firmly established It is commonly taught that the habit of chewing straw leads to infection, but *Actinomyces bovis* has never been isolated from vegetation. On the other hand, the organism is known to be commonly present in and about carious teeth, in dental scum, and in crypts of tonsils, and it is reasonable to assume that the infection disseminates from these areas

**Diagnosis**—The *clinical manifestations* of infection fall into three categories depending upon the region of the body affected The cervicofacial region is most frequently involved, comprising about 60 per cent of the cases The thoracic and abdominal regions are involved next in frequency and comprise together about 40 per cent of the cases The cervicofacial type is frequently associated with dental defects or accidents and is a chronic infection which usually remains localized and which can be treated successfully In the thoracic and abdominal types the prognosis is poor The primary lesion in the thoracic type is in the lung The actinomycetes are either inhaled directly into the lung or spread by aspiration from a neighboring focus of infection in the mouth The pulmonary lesion may resemble a tuberculous infection but there are definite differences which aid in the differential diagnosis In pulmonary actinomycosis the lower lobes are first involved and there is never a spread to the hilar lymph nodes Cavity formation is rare. The infection spreads by continuity and frequently invades the diaphragm and the chest wall In abdominal actinomycosis the primary lesion is often in the appendix In all cases there are draining sinuses and at autopsy abscesses are frequently found in the liver Meningitis and endocarditis rarely occur Generalized actinomycosis from hematogenous spread has been reported

The diagnosis of actinomycosis is established by finding the organism in the pus in the form of very characteristic "sulfur granules" These granules vary in size, have a radiating lobulated structure and are usually yellow in color They are best observed with the low-power microscope lens Occasionally they are large enough to be identified with the naked eye or with a hand lens The interior of the granule does not stand out sharply, but the clubs at the periphery are very refractile and appear as irregular lines marking the borders of the lobules By crushing the granules between two slides and then staining with Gram's stain the gram-positive branched filaments can be demonstrated These branched filaments make up the interior of the "sulfur granule"

The organism is difficult to culture Pus should be washed with sterile normal salt solution Granules should be recovered with a bacteriological loop, washed again in sterile normal salt solution and then placed in thioglycollate media and incubated at 37° C The inoculated tube should be retained for four weeks before discarding Colonies appear as fluffy masses of mycelium

*Treatment*—Treatment for the most part is unsatisfactory and consists of indicated *surgical drainage*, the administration of *potassium iodide* to the point of intolerance and *x-ray therapy* There are numerous clinical notes in the literature proclaiming the effectiveness of the *sulfonamides*, particularly sulfanilamide,<sup>28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38</sup> sulfapyridine,<sup>34, 39, 40</sup> and sulfadiazine<sup>38, 41</sup> In the majority of these reported cases surgical measures, iodide and x-ray therapy supported the sulfonamide therapy and it is impossible to ascribe the entire clinical improvement to the action of the sulfonamides The reported results on the use of *penicillin*<sup>42, 43, 44</sup> are no more impressive than the results reported for other therapeutic measures It must be concluded that necessary surgical intervention, adequate x-ray therapy and intensive iodide administration are essential adjuncts to either sulfonamide or penicillin therapy if optimal results are to be obtained in the treatment of this chronic infection

*Actinomycosis Due to Nocardia Asteroides*—In approximately 10 per cent of the cases of clinical actinomycosis the causative organism is the aerobic, acid-fast actinomycete, *Nocardia asteroides* Throughout the English and American literature the term "streptotrichosis" is frequently used to describe the clinical manifestations produced by *Nocardia asteroides* The term is confusing and should be abandoned

*Diagnosis*—*Nocardia asteroides* commonly infects the lungs and quite frequently disseminates by way of the blood stream to the brain The clinical manifestations of pulmonary actinomycosis due to *Nocardia asteroides* are identical to those due to *Actinomyces bovis* Because *Nocardia asteroides* fails to produce granules and because it is acid-fast there may be difficulty in differentiating it from the tubercle bacillus In contrast to the tubercle bacillus, treatment with sodium hydroxide kills the acid-fast actinomycetes This fact is of practical importance in differentiating actinomycosis due to an acid-fast actinomycete and tuberculosis, because guinea pigs fail to develop lesions following the injection of sputum containing acid-fast actinomycetes which has been treated with sodium hydroxide Fresh sputum injected into guinea pigs will produce lesions from which can be recovered the branching acid-fast organisms typical of *Nocardia asteroides* Drake and Henrici<sup>45</sup> have recently demonstrated that a specific hypersensitivity develops following an infection with *Nocardia asteroides* which can be demonstrated by skin testing with the protein fraction of the organism The skin test, therefore, is of further assistance in the differential diagnosis

*Treatment*—The treatment for actinomycosis due to *Nocardia asteroides* is identical to that for actinomycosis due to *Actinomyces bovis*. In other words, there is no specific treatment. Sulfonamides or penicillin used concomitantly with iodide and x-ray therapy and necessary surgical drainage will produce optimal clinical results.

## BIBLIOGRAPHY

- 1 Keeney E. L. Bull. Johns Hopkins Hosp., 73 379 1943
- 2 Keeney E. L. and Broyles, E. N. Bull. Johns Hopkins Hosp., 73 479 1943
- 3 Keeney E. L., Ajello, L. and Lankford, E. Studies on Common Pathogenic Fungi and on *Actinomyces bovis*. I In Vitro Effect of Fatty Acids Bull. Johns Hopkins Hosp., Dec., 1944
- 4 Keeney E. L., Ajello L. and Lankford, E. Propionate and Undecylenate Ointments in the Treatment of *Tinea pedis* and an In Vitro Comparison of Their Fungistatic and Antibacterial Effects with Other Ointments Bull. Johns Hopkins Hosp., Dec., 1944
- 5 Schenck, B. R. Bull. Johns Hopkins Hosp., 9 286, 1898
- 6 Hektoen L. and Perkins, C. F. J. Exper. Med., 5 77 1900.
- 7 Beummann L. de On Sporotrichosis Brit. M. J., 2 289 1912
- 8 Moore, J. J. and Davis, D. J. J. Infect. Dis., 23 252 1918
- 9 Keeney E. L., Ajello, L. and Lankford E., Studies on Common Pathogenic Fungi and on *Actinomyces bovis*. II In Vitro Effects of Sulfonamides Bull. Johns Hopkins Hosp., Dec., 1944
- 10 Keeney E. L., Ajello, L. and Lankford, E. Studies on Common Pathogenic Fungi and on *Actinomyces bovis*. III. In Vitro Effect of Penicillin. Bull. Johns Hopkins Hosp., Dec., 1944
- 11 Dickson, E. C. Calif. & West. Med., 47 151 1937
- 12 Dickson, E. C. and Gifford, M. A. Arch. Int. Med., 62 853 1938
- 13 Wernicke, R. Centralbl. f. Bakt., 12 859 1892
- 14 Emmons, C. W. Pub. Health Rep., 57 109, 1942.
- 15 Gilchrist, T. C. Bull. Johns Hopkins Hosp., 1 269 1896
- 16 Gilchrist, T. C. J. Exper. Med., 3 53, 1898
- 17 Martin D. S. and Smith, D. T. J. Lab. & Clin. Med., 21 1289, 1936
- 18 Martin D. S. Am. Rev. Tuberc., 39 275 1939
- 19 Busse, O. Virchow's Arch. f. Path. Anat., 140 23 1895
- 20 Buschke, A. Deutsche Med. Wochenschr., 21 14 1895
- 21 Pedrosa A. and Gomes, J. M., Ann. Paulistas Med. e Cir. y Especialidades, 11-53 1920.
- 22 Lane, C. G. J. Cutan. Dis., 33 840, 1915
- 23 Medlar E. M. Mycologia, 7 200 1915
- 24 Medlar E. M. J. Med. Res., 32 507 1915
- 25 Darling S. T. J.A.M.A., 46 1283 1906
- 26 De Monbreum W. A. Am. J. Trop. Med., 14 93 1934
- 27 De Monbreum, W. A. Arch. Dermat. & Syph., 31 831 1935
- 28 Poulton, E. P. Proc. R. Soc. Med., 31 164 1937
- 29 Walker O. Lancet, 1 1219 1938
- 30 Miller E. M. and Fell, E. H., J.A.M.A., 112 731, 1939
- 31 MacCharles, M. R. and Kippen, J. W. Canad. M. A. J., 41 490 1939
- 32 Hall W. E. B. J.A.M.A., 112 2190 1939
- 33 Sudler M. T. and Johnson, C. B. J. Kansas M. Soc., 40 330 1939
- 34 Dorling G. C. and Eckoff N. L., Lancet, 2 707 1940
- 35 Christopher F. and Karakin, J. E. Am. J. Surg., 50 371 1940
- 36 Wilkinson E. E. J. Pediat., 18 805 1941
- 37 Dobson, L., Holman E. and Cutting W. J.A.M.A., 116 272, 1941

- 38 Lyons, C, Owen, C R and Ayers, W B Surgery, 14 99, 1943
- 39 Ogilvie, W H Brit M J., 2 254, 1940
- 40 Mitchell, H S Canad M A J, 46 584, 1942
- 41 Hallenbeck, W F and Turnoff, D J A M A., 123 1115, 1943
- 42 Keefer, C S, Blake, F G., Marshall, E K., Jr, Lockwood, J S and Wood  
W B, Jr J.A.M.A., 122 1217, 1943
- 43 Herrell, W E J.A.M.A., 124 622, 1944
- 44 Lyons, C J.A.M.A., 123 1007, 1943
- 45 Drake, C H and Henrici, A T Am Rev Tuberc., 48 184, 1943

# THE DIAGNOSIS AND TREATMENT OF BRUCELLOSIS

WESLEY W SPINK, MD, F A C P \*  
AND WENDELL H HALL, MD †

TOWARD the end of the last century, a young army surgeon was attached to the British forces on the Island of Malta. While there, his wife, two sisters and himself contracted brucellosis. Returning to England to convalesce, Hughes wrote and published a monograph in 1897, now considered a classic, on "Mediterranean, Malta or Undulant Fever." The introductory sentence of the preface states, "When the writer arrived in Malta towards the end of the year 1890, for a six years tour of service in that place, he found that his medical work would chiefly consist, during the greater part of the year, of treating a fever about which no two medical officers appeared to agree, respecting its cause, treatment or even name." Almost fifty years have elapsed since the foregoing statement was made, and in the intervening time the cause of brucellosis has been definitely established, but physicians are still perplexed by diagnostic and therapeutic problems relating to this disease. This confusion is not due to a lack of interest in the subject. Many investigations, both experimental and clinical, have been made, several important reports have appeared, including two informative monographs,<sup>1, 2</sup> but still the question is asked, how may one establish an unequivocal diagnosis of brucellosis? And if an accurate diagnosis is established what therapeutic procedure shall one carry out for a patient with the disease?

The purpose of this clinic is to summarize briefly the outstanding features of the disease, to evaluate the diagnostic procedures now available, and to present today's therapy. For information we have drawn largely from our clinical experience with this disease at the University of Minnesota Hospitals during the last seven years, and from the documented observations of other investigators.

## ETIOLOGY AND MODES OF TRANSMISSION

As will be pointed out shortly, the accurate diagnosis of brucellosis often calls for a correlation of many factors including certain epidemiologic data. Microorganisms belonging to the genus *Brucella* are responsible for the disease. They are small, motile or nonmotile, gram-

---

From the Division of Internal Medicine, University of Minnesota Hospitals and Medical School, Minneapolis, Minnesota.

Associate Professor of Medicine, Department of Medicine, University of Minnesota Medical School.

† Clinical Assistant in Medicine, Department of Medicine, University of Minnesota Medical School.

negative rods with many coccoid forms. At the present time, three species are recognized, *Brucella abortus* (cattle), *Brucella suis* (swine) and *Brucella melitensis* (goat). It is not unlikely that these three species have had a common origin, and that specific biological or metabolic characteristics for each species have arisen as a result of adaptation to different hosts. It is important that these differences in species should be kept in mind by the clinician since they are frequently reflected in the severity of the disease and also in the results of therapy. While cattle, swine and goats constitute the large reservoir for *Brucella*, other animals are known to be naturally infected. These include sheep, horses, mules, deer, buffaloes, dogs, rabbits and poultry.<sup>3</sup> Nevertheless, cattle, swine and goats constitute the main sources of disease for human beings. It is generally agreed that *Brucella suis* is more invasive for human tissue than *Brucella abortus*. It should be borne in mind that each of the species may reside in hosts other than that for which it is named. Thus, an epidemic of human disease due to *Brucella suis* has arisen from the ingestion of raw cow's milk.<sup>4</sup> Horses have been shown to be infected with *Brucella abortus*, and cases of human infection have been traced to this source.<sup>5, 6</sup>

The disease is transmitted to human beings via the gastrointestinal tract and through the skin. One of the most common sources of infection is the ingestion of contaminated milk or milk products. Although this mode of transmission undoubtedly results in many infections, it is surprising how difficult it is to establish the disease both in human subjects and in lower animals by the experimental feeding of large doses of viable *Brucella*.<sup>7</sup> This probably accounts for the many instances of subclinical infections with the development of hypersensitivity to *Brucella* antigen. The second common method of transmission is by direct contact with contaminated or infected material with entrance of the bacteria through the skin. It has been demonstrated experimentally that guinea pigs may be infected by applying cultures to the normal or abraded skin.<sup>8</sup> Human beings have been experimentally infected in a similar manner through abraded skin but not through the intact skin.<sup>7</sup> Although human beings may excrete viable *Brucella* in the feces or urine for long periods of time, no authentic human to human infection has been recorded. Nevertheless, soiled bed linen may possibly serve as a basis for a hand to mouth infection. *Brucella* organisms have been recovered from the milk of a nursing mother,<sup>9</sup> but have been isolated from the sputum very rarely. While biting flies and mosquitoes have been shown to transmit the disease experimentally, no natural spread has been traced to this source.<sup>3</sup> Another possible route of infection is through the respiratory tract following the inhalation of dust containing *Brucella*. Microorganisms may remain viable in shaded dust or soil for one to two months.<sup>10</sup> Monkeys have been experimentally infected following the inhalation of dust containing *Brucella melitensis*.<sup>11</sup> It is also of importance that *Brucella* organisms

have been found to be viable after two months in Roquefort cheese, four months in refrigerated butter, and ten days in refrigerated milk. *Brucella suis* has withstood refrigeration in hogs' spleens for thirty days at  $-10^{\circ}$  degrees F., and in meat-curing brine for forty-five days.<sup>10</sup>

An analysis of thirty-five cases of brucellosis seen at the University of Minnesota Hospitals shows that probably all were due to *Brucella abortus*. This is associated with the fact that twenty-two, or 63 per cent, of the patients consumed raw milk obtained from infected cattle, and seven patients, or 20 per cent, handled infected material from aborting cattle. With the exception of one packing plant employee, the source of the infection could be traced.

### CLINICAL MANIFESTATIONS OF BRUCELLOSIS

The usual procedure in discussing the clinical features of brucellosis is to divide the analysis into a consideration of the acute and chronic phases of the disease. This division is sound provided one does it in relation to the time factor, that is, acute brucellosis should indicate a symptom complex of short duration, whereas chronic brucellosis should imply the presence of symptoms for a period of several weeks or months, and in a few instances, for years. An explanation of an obvious and well recognized classification of disease is given because, too often, chronic brucellosis is described as an ill-defined entity with few or no localizing signs. Most of the errors and difficulties in diagnosis relate to the chronic cases, and the diagnosis is frequently made upon the basis of inadequate clinical and laboratory data. As will be described shortly, cases of chronic brucellosis may exhibit many of the clinical manifestations usually associated with the acute stage of disease. In addition, the chronic cases may have important localized signs of the infection.

**Acute Brucellosis**—The incubation period varies from five to twenty-one days with an average of ten to fourteen days. The common signs and symptoms together with the relative frequency have been excellently summarized by Hardy and his associates<sup>11</sup> based on an analysis of 300 case studies in Iowa. A review of a smaller group of cases at the University of Minnesota Hospitals was in agreement with these observations.<sup>12</sup> The onset of clinical brucellosis may be sudden or insidious. Clinical symptoms resembling acute respiratory infections are not uncommon, and diagnoses such as "la grippe," 'influenza,' or 'intestinal flu' are often made. The *febrile response* may be marked and may be sustained as in typhoid fever, or intermittent, as in pyogenic infections. In milder cases, a low-grade fever may be present. The *pulse rate* is often relatively slow in proportion to the fever. The outstanding complaint in all cases is *weakness*, which in the mild cases may be the only subjective complaint. *Sweating*, moderate to profuse, is experienced by a majority of individuals who contract the disease. *Chilliness*, often a symptom observed during the period of invasion



frequently persists and frank chills may usher in the daily rise of temperature seen in the more severe cases *Pain* usually takes the form of a generalized malaise and tends to persist in the ambulatory patient, and to be aggravated by physical exertion. The pain, when it is localized, is generally manifested by headache, arthralgia, lumbar pain, or abdominal pain. The latter may be prominent and has in more than one instance led to an erroneous surgical diagnosis. Simpson<sup>14</sup> has information on twelve appendectomies and two cholecystectomies carried out in patients with brucellosis, resulting in normal pathological specimens. *Gastrointestinal disturbances* usually take the form of anorexia and constipation. Diarrhea is rare. *Painful swelling of the testicles* is apparently not infrequent, though we have not recognized a single instance in our series. Of the exhibited *neurologic disorders*, insomnia, restlessness and irritability are most common, while delirium and coma are rare.

*Subclinical Infections*—It is becoming more and more apparent that there are many individuals whose tissues are invaded by *Brucella*, but the infections are so mild that they escape detection. Furthermore, symptoms may be entirely absent, and yet tissue sensitivity to the microorganisms has been induced, and serologic tests will reflect such an invasion. There are several reports of subclinical infections occurring in epidemics of brucellosis involving individuals who have ingested contaminated milk.<sup>15, 16, 17, 18, 19</sup> These mild or subclinical infections are more likely to occur following invasion with *Brucella abortus*. In this respect brucellosis is like tuberculosis. It is this group of patients who present a difficult problem in differential diagnosis at a late period when they present themselves to a physician with ill-defined symptoms and possess immunological evidence of brucellosis. It is important to bear in mind that the subclinical type or ambulant case of brucellosis may have a demonstrable bacteremia.<sup>20</sup>

*Chronic Brucellosis*—Chronic brucellosis may be the sequela of an acute, febrile illness, which may or may not have been recognized as brucellosis initially, or the disease may have had an insidious onset originally, and the ill-defined symptoms have persisted over a long period of time. As Evans<sup>21, 22</sup> has pointed out, many of the patients with chronic brucellosis have been diagnosed as having neurasthenia. The outstanding clinical features are a multiplicity of physical and mental complaints with few or no localizing signs. The most common complaint is *weakness*. The patients tire readily. A low-grade fever may be present, usually intermittently. There are *vague aches and pains* referable to the skeletal system and muscles. Low back pain is frequently present. *Mental depression* occurs, as well as *nervousness and emotional instability*. *Tachycardia, palpitation* and *sweats* appear following exertion. Physical examination may reveal splenomegaly and hypotension in a small group of cases. Little wonder then that chronic brucellosis is confused with neurasthenia or "constitutional inade-

quacy" On the other hand, patients with neurasthenia or psychoneurosis are more often labeled as having chronic brucellosis on the basis of the symptomatology and inconclusive laboratory data The difficulties encountered in making an unreserved diagnosis of chronic brucellosis will be discussed subsequently in relation to the laboratory aids in diagnosis.

### PATHOLOGY OF BRUCELLOSIS

The histopathology of brucellosis has not been clearly defined Forbus<sup>23</sup> has recently summarized the information at hand as follows He described three fatal forms of the disease, namely, the septicemic or relatively acute form, the focal or localized form of infection, which is also relatively acute, and the chronic lymphogranulomatous type. There are no distinguishing features in the septicemic type. The localized forms include vegetative endocarditis, meningitis, orchitis and osseous lesions The lymphogranulomatous form demonstrates what Forbus believes to be characteristic lesions for brucellosis The basic reaction involves the reticulo-endothelial system with a proliferation of large mononuclear cells This is succeeded by necrosis and then a proliferation of fibroblasts or a scar composed of reticulum Multinucleated giant cells are seen which closely resemble the Sternberg or Dorothy Reed cells of Hodgkin's disease In fact, Parsons and Poston<sup>4</sup> described the lesions in a fatal case of granulomatous brucellosis as being indistinguishable from those found in Hodgkin's disease. Thus excited the interest of the Duke University investigators, and in a subsequent report<sup>25</sup> they recorded the isolation of *Brucella melitensis* from the blood or lymph nodes in fourteen consecutive cases of Hodgkin's disease, whereas in a control series of sixty-seven cultures of lymph nodes obtained from individuals without Hodgkin's disease, only one yielded *Brucella*<sup>26</sup> While the Duke workers have implied a possible etiologic relationship between Hodgkin's disease and brucellosis, much more confirmatory evidence from other centers is desirable concerning the incidence of brucellosis in patients having Hodgkin's disease.

In two fatal cases of brucella endocarditis due to *Brucella abortus* studied at the University of Minnesota Hospitals,<sup>27 28</sup> granulomatous lesions of the reticulo-endothelial system were not observed, but in several organs a mononuclear type of cellular reaction was noted

### LOCALIZING SIGNS OF BRUCELLOSIS

The following brief discussion emphasizes the protean manifestations of brucellosis, and may be of aid in recognizing the disease.

**Ocular Manifestations.**—It is becoming more and more apparent that diseases of the eye of obscure origin may be related to brucellosis Chronic uveitis is one of these conditions<sup>30 31</sup> Brucellosis may involve the internal ocular muscles, the cornea, the uveal tract, the retina and

the optic nerve Therefore, errors in vision which at first would not appear to be due to an infection may be attributable to this disease

**Oral Manifestations**—*Brucella* organisms have been recovered from the ulcerated lesions of the mucous membrane of the mouth and the oral pharynx<sup>32</sup> Some individuals recommend a careful culture of the tonsils and oral pharynx in every person suspected of having brucellosis This does not appear to be unreasonable since brucellosis is a disease which involves the reticulo-endothelial system, and invasion of the tissues is frequently through the oral pharynx

**Pulmonary Manifestations**—Patients with brucellosis, not infrequently, may have a persistent cough An atypical form of pneumonia may occur *Brucella melitensis* has been isolated from sputum<sup>33</sup> and from empyema fluid<sup>34</sup> A review of the literature on the pulmonary changes in brucellosis has been reported by Bogart<sup>35</sup> We have encountered a fatal case of brucella endocarditis, in which pneumonia was present, and the outstanding histologic feature was an exudate consisting almost entirely of mononuclear cells We have also seen one patient with a pleural effusion in association with brucellosis

**Vegetative Endocarditis**—This appears to be a relatively uncommon manifestation of brucellosis, and yet we have encountered two fatal cases at the University Hospitals in seven years<sup>27, 28</sup> One of the important diagnostic features is that the patients may have a high titer of agglutinins in the blood, a bacteremia, and yet the intradermal injection of *Brucella* antigen may provoke no local reaction An analogous phenomenon is observed in patients having vegetative endocarditis due to streptococci of the viridans type Whenever a patient has the manifestations of bacterial vegetative endocarditis, and routine bacteriological procedures have failed to reveal the etiologic microorganisms, investigations should be directed toward excluding *Brucella* as the possible cause In this manner, our two cases of brucella endocarditis were resolved

**Biliary Tract**—Brucellosis may involve the biliary tract *Brucella* have been isolated from the bile and gallbladder in patients with cholecystitis<sup>36</sup> and have been implicated as a cause of hepatitis<sup>37</sup> Since *Brucella* have an affinity for the reticulo-endothelial system, it is not surprising that hepatitis may be observed It is not unlikely that cirrhosis of the liver may also occur We have seen a few instances of portal cirrhosis in patients in whom a presumptive diagnosis of brucellosis had been made on the basis of immunologic reactions Although we have cultured the bile of several patients having brucellosis with bacteremia, we have not isolated the organisms from the bile Zaus and Espev<sup>38</sup> are of the opinion that patients having a previously damaged liver are more likely to show further evidence of hepatic damage from brucellosis

**Manifestations Referable to the Male and Female Genitalia, and Relation of Brucellosis to Human Abortions**—A commonly reported manifes-

tation of brucellosis in males is orchitis resulting in swelling of the testicles. However, this has not been observed in our series at the University Hospitals. Pelvic inflammations in females, particularly tubo-ovarian abscesses, have also been reported. Again, no proven case has been encountered at the University Hospitals.

While brucellosis in pregnant lower animals is frequently associated with spontaneous abortion, the incidence of undoubted cases in human beings is rare. Carpenter and Boak<sup>39</sup> have reviewed the literature on the subject, and report the isolation of *Brucella abortus* from a human fetus, and French workers<sup>40</sup> have isolated *Brucella melitensis* from the tissues of a fetus and the blood of a mother. While some authorities in this country<sup>41</sup> believe that miscarriages occur with frequency in women having chronic brucellosis, more precise bacteriologic data are needed. It would be highly desirable for some of the larger centers, particularly those in endemic areas, to institute studies of all instances of unexplained human miscarriages in an attempt to establish the incidence of such an association. We have not observed a single proven case of this type at the University Hospitals.

**Lymphadenopathy.**—Reference has already been made to the observation that enlargement of the superficial lymph nodes occurs in brucellosis; that *Brucella* may be cultured from lymph nodes, and that the histology of the nodes in some instances is not unlike that seen in Hodgkin's disease. An analysis of the literature by Bloomfield<sup>42</sup> would indicate that lymphadenopathy is not an uncommon manifestation of brucellosis. In a series of thirty-five cases at the University Hospitals, nine of the patients, or 25.7 per cent, had enlarged peripheral lymph nodes. Attention has recently been called to the clinical similarity between some cases of infectious mononucleosis and brucellosis.<sup>43</sup> In both diseases, lymphadenopathy may be a prominent feature.

**Splenomegaly.**—When present, a palpable spleen constitutes a very helpful manifestation of brucellosis. In our own series of thirty-five proven cases, the spleen was palpated at some time during the course of their illness in fourteen of the patients, or in 40 per cent. The spleen is more likely to be palpable during the acute phase of the disease.

**Skin Lesions.**—Various types of dermatologic lesions have been described as occurring during the course of brucellosis.<sup>2</sup> In general, these consist of macular lesions, maculopapular lesions, localized and generalized erythema, purpura, lesions simulating erythema nodosum, lesions indistinguishable from the "rose spots" of typhoid fever, and ulcerating and eczematous lesions. We have observed one patient with acute brucellosis and bacteriemia who had a butterfly type of erythematous lesion over the bridge of the nose and cheeks, not unlike that seen in acute disseminated lupus erythematosus. Huddleson<sup>1</sup> has recorded two types of skin lesions as occurring in veterinarians. One consists of an erythema of the arm, which appears after the manual removal of placentae from aborting cows, and is associated with itching or

burning but no desquamation or exudation. This type is considered to be due to a hypersensitivity to a placental protein. The second type is due to a specific allergy resulting from a *Brucella* infection, and it displays discrete, elevated, reddish lesions, which burn and itch, and later ulcerate. Systemic reactions may accompany the skin lesions. The lesions may last for three to four weeks.

The following case illustrates an acute *Brucella* infection with a pronounced skin eruption, in which the illness terminated rapidly.

**CASE I**—A 28 year old white man, an insurance agent, was in good health until four days before entry to the University Hospitals. The onset of his illness was marked by a chill which lasted thirty minutes. There was no preceding upper respiratory infection. On the following day he continued to have chilly sensations with generalized stiffness of the muscles. Two days after the onset, a rash appeared on the skin of his upper and lower extremities without itching or tenderness. He then developed a cough productive of mucoid, frothy material. There was no chest pain. On the day of entry he had a chill lasting one hour. He perspired profusely and complained of slight rigidity of the neck. About two weeks prior to his illness he drank some water from a questionable source. There was no history of tick bites.

Examination revealed a febrile patient appearing acutely ill. He was perspiring profusely. The sclerae were injected. The pharynx appeared normal. The heart and lungs were within normal limits. The abdomen was slightly distended. A tender and soft spleen was palpated about 3 cm. below the right costal margin. The skin over the arms, legs and abdomen was involved with a slightly elevated, discrete, pink eruption. The lesions were of different sizes and faded on pressure. Similar lesions were present on the soles of the feet, around the ankles, a few on the back, but none on the palms of the hands. The superficial lymph nodes were not enlarged.

On the day after entry the patient complained of pain in the joints of the right ankle and right wrist. He was acutely ill. An intradermal test with vaccine prepared from *Brucella abortus* showed a slightly positive reaction at the end of forty-eight hours. The initial leukocyte count was 3300 cells, with a differential count of 60 per cent polymorphonuclear neutrophils and 40 per cent lymphocytes. The leukopenia persisted throughout his illness. An erythrocyte sedimentation rate was within normal limits. His blood cultures remained sterile. Agglutinins for *Brucella*, *B. typhosus*, and *B. tularensis* were absent on the second and fifth hospital days, but on the ninth day, a titer of 1 to 1280 for *Brucella abortus* was obtained, no agglutinins for other pathogens were present. Guinea pigs injected with the patient's blood shortly after entry failed to show evidence of an infection, and when sacrificed, *Brucella* were not cultured from any of the organs.

Forty-eight hours after entry to the hospital the patient was given sulfanilamide in doses of 1 gm. every six hours, after an initial dose of 4 gm. He received a total of 18 gm. in five days. Coincident with this therapy his condition improved rapidly, and the skin eruption faded. He left the hospital nine days after entry. This patient was seen at intervals during the following five years. There has been no recurrence of his illness, and his blood has failed to show the presence of agglutinins for *Brucella*.

**Nervous System**—De Jong<sup>44</sup> has reviewed the literature pertaining to the involvement of the nervous system in brucellosis. Headache is a common manifestation. Peripheral neuritis may occur, which may persist for weeks. Unexplained instances of peripheral neuritis should oc-

casion an investigation for the possibility of brucellosis. Invasion of the central nervous system may produce encephalitis, meningitis and myelitis. *Brucella* have been isolated from the cerebrospinal fluid.

**Joint Manifestations.**—Pain referred to the joints is a common manifestation of brucellosis. While the tissues surrounding the joints may be swollen, reddened and tender, and an effusion may be present, brucellosis rarely, if ever, causes a chronic arthritis.<sup>45</sup> Intermittent hydrarthrosis, particularly of the knee joint, has been reported, and *Brucella* organisms have been isolated from the synovial fluid.

**Spondylitis.**—A common manifestation of both acute and chronic brucellosis is pain over the spine, involving especially the lumbosacral areas. In many instances the precise nature of this pain is difficult to ascertain, but careful roentgenologic studies of the site of pain should be made in order to exclude the possibility of spondylitis. The lesion begins in the marrow of the vertebra and the intervertebral disks are involved secondarily. The lesion of brucellosis must be distinguished from a tuberculous process, and osteomyelitis due to pyogenic bacteria. The condition has been reviewed by Bishop,<sup>46</sup> and Feldman and Olson<sup>47</sup> have described specific spondylitis in swine due to *Brucella*. These lesions were discovered only after careful dissection and occurred in apparently healthy animals.

We have recently reviewed the literature on spondylitis due to *Brucella*, and we have found sixty-eight cases recorded. At the University Hospitals, we have studied five patients with *brucella* spondylitis.

The following case demonstrates the chronicity of brucellosis and the late development of spondylitis in a patient who had a bacteremia. At first, the patient was considered to have a tuberculous lesion of the spine for reasons to be detailed.

**CASE II.**—A 25 year old white male employed as a shipping clerk entered the University Hospitals because of fever, generalized muscular pain, night sweats and lumbar pain radiating into both thighs. He had been drinking raw milk, but there was no demonstrable evidence of Bang's disease in the cattle from whom the milk was obtained. The patient's mother and brother had both died of tuberculosis in his home. His illness began about eleven months before entry when he developed weakness, anorexia and a failure to maintain his normal weight. Four months later he developed the symptoms which prompted his entry to the University Hospitals.

On entry the patient appeared well developed, fairly well nourished, and chronically ill. His temperature was 99.6 F. There was no lymphadenopathy. The lungs were clear and there were no cardiac abnormalities. The liver and spleen were not palpable. There was tenderness upon percussion over the spinal processes of the second, third and fourth lumbar vertebrae. There was spasm of all the lumbar muscles, and the lumbar spine was held rigid.

The leukocyte count was 8100 cells, with 66 per cent polymorphonuclear neutrophils, 33 per cent lymphocytes and 1 per cent monocytes. The sedimentation rate of the erythrocytes was markedly accelerated. The Wassermann test was negative. The calcium, phosphorus and phosphatase values of the blood were normal. Agglutinins were present in his serum for *Brucella abortus* in a titer of

1 to 2580, and an intradermal test with *Brucella* vaccine provoked a marked reaction. The Mantoux test was strongly positive. Blood cultures for *Brucella* taken at the time of his admission remained sterile. However, it was learned that his physician had submitted a specimen of blood to the laboratories of the Minnesota State Board of Health seven months previously and *Brucella abortus* was found to be present.

Roentgenologic examination of the lungs was normal, but films of the lumbar region revealed considerable destruction of the intervertebral disk between the second and third lumbar vertebrae and destruction of the bodies of these two vertebrae. There was some enlargement of the shadow of the left psoas muscle suggesting the possibility of a psoas abscess. There was also an area of rarefaction in the right sacroiliac joint suggestive of a destructive form of arthritis.

An attempt to aspirate material for cultural purposes from the left psoas region was unsuccessful. The patient was given sulfanilamide in an initial dose of 4 gm and then 1 gm every six hours. He received a total of 56 gm in seven days. This maintained a blood level of 10 mg per 100 cc. Coincident with this therapy, his temperature gradually approached normal. A plaster-of-paris body jacket was applied, which afforded complete relief of his back pain. He left the hospital in a body cast forty-five days after entry.

Three months later the patient returned to the hospital. He had no fever or back pain and had gained 20 pounds in weight. There was slight tenderness upon percussion over the third lumbar spinous process. The leukocyte count was 5900 and the erythrocyte sedimentation rate was normal. Roentgenologic examination of the lumbar spine showed increased destruction of the intervertebral disk between the second and third lumbar vertebrae, but there was less decalcification of bone. A Taylor body brace was applied, and he was permitted to return to work eleven months after his first entry to the hospital. Soon thereafter he discarded the brace and he has been doing heavy work without having back pain. There has been no remission of his illness in a period of three years.

#### LABORATORY AIDS IN THE DIAGNOSIS OF BRUCELLOSIS

As pointed out by Foshay,<sup>48</sup> clinicians are leaning too heavily upon laboratory procedures for making a correct diagnosis of brucellosis. In a consideration of each suspected case it is necessary to bear in mind the epidemiology of the disease, the many manifestations of brucellosis, and then correlate them with the various laboratory data. As part of the investigations on brucellosis which we have been carrying out in our clinic, Miss Suzanne Agnew<sup>49</sup> performed a number of laboratory procedures in eighty-five cases suspected of being brucellosis. There were forty-nine control patients. These procedures were carried out simultaneously and included the following: complete hematologic studies including hemoglobin determinations, erythrocyte levels, and total leukocyte and differential counts. Agglutination titers were determined simultaneously by the "rapid" slide method of Huddleson and the multiple tube or macroscopic method. The complement fixation test was evaluated. Opsonocytophagic indices were performed according to the method of Huddleson,<sup>50</sup> and with a second test suggested by Jersild.<sup>51</sup> Two different media for culturing *Brucella* in blood were investigated. Intradermal tests were performed with a heat-killed vaccine, with "brucellergin," and with a purified protein derivative of *Brucella*.

The following discussion is based largely upon the results of the foregoing study and the investigations of others

**Blood Leukocytes.**—In several instances, our attention has been called to the possibility of a febrile patient having brucellosis because of the presence of a lymphocytosis in the peripheral blood. While it is often assumed that a leukopenia is present, this is by no means the rule. The total leukocyte count may be normal, below normal or actually elevated. We have encountered levels of 15 000 cells per cubic millimeter. The important factor is the presence of a relative or absolute rise in the lymphocytes. This diagnostic feature has been excellently presented by Calder and his associates.<sup>52</sup> We are of the opinion that the erythrocyte levels or hemoglobin concentrations are not of particular value.

**Sedimentation Rate of Erythrocytes.**—Brucellosis is one of the few infectious diseases in which the sedimentation rate may remain normal throughout the course of the disease. This factor may constitute additional evidence favoring a diagnosis of brucellosis.

**Agglutinins.**—Clinicians rely considerably upon the presence of agglutinins in the blood serum for making a diagnosis of brucellosis and rightly so. The test is of value when used in conjunction with the clinical findings and other laboratory data. There are several points to consider in evaluating the results of the test. First, an appreciable number of patients with active brucellosis may not have agglutinins in the blood even in the presence of suppurative lesions. This may be related to the invading strain of *Brucella*, which may be a poor antigen, or may be due to the failure of the patient to respond. Castaneda and his associates<sup>53</sup> observed that about 10 per cent of their patients with bacteremia had no agglutinins. Second, it may take several days or weeks after the onset of an acute illness before agglutinins may be detected. Third, the titer may fluctuate from time to time, agglutinins being absent on some occasions. Fourth, the antigen used for the agglutination test is of some importance. Thus, one laboratory may report the presence of agglutinins in a specimen of blood while another laboratory may not, each using a portion of the same serum for the test.

The question is frequently asked as to what titer of agglutinins is diagnostically significant as far as active disease is concerned. One cannot give an arbitrary titer as being diagnostic in itself. In general, the higher the titer, the more likely is the clinician to demonstrate a bacteremia. This has been our experience and that of others.<sup>54</sup> Repeated tests should be done on a patient suspected of having the disease.

It is well recognized that agglutinins will appear in the blood in normal subjects following the intradermal injection of *Brucella* antigen. This response is usually in evidence during the second or third week after the test. Usually titers less than 1 to 100 are obtained. At least, that has been our observation as well as that of Kirby and Rantz.<sup>55</sup> This applies to patients having a negative or positive dermal reaction. On the other hand, Menefee and Poston<sup>56</sup> observed that positive dermal reactors may have a considerable elevation of the agglutinin titer especially during the third week after the injection. We do not believe that the titer of the agglutinins following an intradermal test with antigen is of diagnostic significance as to whether or not the patient has an active disease process.

It is of significance that in an individual whose tissues have been invaded by *Brucella*, with or without clinical evidence of the disease, agglutinins may persist in the blood for months or years. Under these circumstances a nonspecific rise in the titer of the agglutinins may shortly follow an unrelated febrile illness, such as streptococcal sore throat.<sup>56</sup> It is this type of phenomenon which lends confusion to the diagnosis of chronic brucellosis.

In summary then, the agglutination test is a valuable diagnostic aid in brucellosis only when correlated with other laboratory data, the clinical illness, and



epidemiologic factors In performing the test, the "rapid" slide agglutination of Huddleson may be used, or the macroscopic tube method Neither test is of any advantage over the other, though we prefer to carry out the latter test

**Complement Fixation Test**—This test has been thoroughly investigated in our clinic and it does not appear to possess any advantage over the agglutination test except that complement-fixing antibodies appear earlier in the blood than agglutinins in some instances This is in accord with the opinion of others<sup>57</sup> Because additional information obtained from the results of the complement fixation reaction is so slight, its routine use is not advocated

**Opsonocytophagic Test**—Much has been written about this diagnostic procedure, still it is surprising what little clinical information may be obtained from its use This applies to its application in the diagnosis of an active infection, and also its use in ascertaining the immune status of the patient A similar conclusion was reached by Wise<sup>58</sup> The test has been completely evaluated in our clinic by Agnew,<sup>49</sup> and the conclusion reached is that the test is of little aid in itself, but may contribute to the diagnosis when used in conjunction with other procedures The standard test requires the use of virulent microorganisms, and there exists a potential danger in its routine use as far as laboratory personnel is concerned There is recent evidence that the test may be performed with killed organisms At present, the opsonocytophagic test is not being used in our clinic

**Skin Test**—This is the most abused diagnostic procedure and provides the clinician with the least reliable information A positive cutaneous reaction following the intradermal injection of *Brucella* antigen should be interpreted in the same light as the tuberculin reaction A positive test does not necessarily imply an active infection or even a past clinical infection It reflects a state of hypersensitivity to *Brucella* antigen in individuals who have had contact with the material at some time in the past As pointed out already, patients may actually have a bacteremia with a *brucella* endocarditis and yet no dermal reaction may be provoked following the injection of the antigen Material widely used in skin testing individuals includes a heat-killed vaccine and brucellergin which is a nucleoprotein fraction of the cells Heat-killed vaccine usually containing cells from the three species of *Brucella* provokes violent local and systemic reactions at times We prefer brucellergin since the reactions are milder In the last two years we have been using the purified protein antigen prepared by Dr Morales Otero<sup>60</sup> of San Juan, Puerto Rico and supplied to us through his courtesy This material produces fewer local and systemic reactions than does the vaccine.

It should be emphasized that in clinical practice the skin test is of little diagnostic aid in itself This has been our experience and has been beautifully shown by the excellent investigations of Heathman,<sup>60</sup> which involved several hundred workers in the larger packing plants of Minnesota The intradermal injection of any *Brucella* antigen may sensitize some normal individuals to the antigen, and may be followed by the development of agglutinins This may be confusing when a patient is seen subsequently by different physicians

Again, the skin test should only be used in conjunction with other procedures, and interpreted with relation to the clinical status of the patient

**Blood Culture**—Specimens of venous blood should be obtained from every patient suspected of having brucellosis and the blood should be added to an appropriate culture medium It is our policy to culture blood every other day for at least three times, particularly in suspected acute causes In chronic cases, cultures of blood may be carried out at less frequent intervals A variety of culture media have been proposed for the isolation of *Brucella* including liver infusion broth During the past few years, the Laboratories of the Minnesota State Department of Health have been handling the blood cultures for the University Hospitals, and the procedure has been highly satisfactory The medium

with 1 per cent sodium citrate Twenty

five cubic centumeters of broth are contained in large vaccine bottles. To each bottle is added 5 cc of blood directly from the patient. Utilizing sterile precautions, 10 per cent of the air in the bottle is replaced by carbon dioxide. This is done because the growth of the species *Brucella abortus* is facilitated by the increased carbon dioxide tension. After incubation for five days at 37° C., subcultures are made upon several dextrose agar slopes, and the tubes incubated further in a jar containing added carbon dioxide. Usually, at the end of forty-eight hours, colonies of *Brucella* may be seen on the agar slants. Occasionally strains of *Brucella abortus* grow very slowly and a longer period of observation may be necessary. Identification of the *Brucella* as a group is made by fermentation tests and by employing a potent anti-*Brucella* serum for the agglutination reaction. The species may be differentiated by the dye method of Huddleson.<sup>1</sup>

In the foregoing manner *Brucella* have been isolated from the blood of acutely febrile patients, and also from the blood of patients who have been chronically ill and afebrile. When a bacteremia has been demonstrated bacteriologically there is no doubt about the diagnosis. During the past seven years, we have cultured the blood repeatedly in well over 100 patients strongly suspected of having brucellosis, and *Brucella*, all of the *abortus* variety have been isolated from only ten individuals. During this time, thirty-five patients have been considered as having the active form of the disease. This means that bacteremia was demonstrated as being present in a little less than one third of the patients.

*Brucella* may also be obtained from human sources other than from the blood. The organisms have been isolated from bile and stools, as well as from urine.<sup>61</sup> Some investigators routinely culture the tonsils in suspected cases, since *Brucella* organisms have been isolated in this manner.<sup>62</sup>

In summary, the practical laboratory aids which we have found applicable to suspected cases of brucellosis are the blood leukocyte and differential counts, the erythrocyte sedimentation rate, and the macroscopic agglutination reaction and cultural studies, particularly repeated cultures of blood. The skin test with appropriate antigen is the least helpful. Other laboratory procedures such as the complement fixation reaction and opsonocytophagic test can only be carried out in certain centers and are not enough of an aid to the clinician to warrant their routine use.

#### BRUCELLOSIS IN CHILDHOOD

It is generally assumed that infants and young children are relatively resistant to *Brucella*. It is well known that it is difficult to establish a well-defined disease in calves and kids with *Brucella*. Certainly, the established incidence of brucellosis in children is less than that encountered in adults. Whether this age distribution means that the disease is generally unrecognized in children, or that young children are resistant to the disease, is difficult to assay. Experience at the University of Minnesota Hospitals would indicate a low incidence of active disease in young children, and when the infection does occur it is usually mild and the disease goes unrecognized. This coincides with the experience of others.<sup>20</sup>

Over a period of seven years, several hundred individuals including children, have been investigated for the presence of brucellosis, and the disease was definitely established as being present in only two

children under twelve years of age The essential clinical features in one of these children are as follows

CASE III—A 6 year old white male was seen with Dr Ralph Platou on the Pediatric Service The child had always enjoyed good health until approximately four months before entry when he developed chickenpox Following this he continued to complain of marked fatigue, and he became more and more listless. He had a daily temperature elevation of 102° to 104° F About three weeks before admission he was seen by Dr Platou who suspected brucellosis because of a palpable spleen as the only localizing physical abnormality Blood sent to the Laboratories of the Minnesota State Department of Health revealed agglutinins for *Brucella abortus* present in a titer of 1 to 640, and a pure culture of *Brucella abortus* was isolated from his blood He was given sulfadiazine over a period of ten days in doses which established a blood level of free sulfadiazine of 11.5 mg per 100 cc

Because improvement was slow, it was decided to admit the patient to the hospital, continue with sulfadiazine therapy, and, in addition, institute treatment with artificial fever by means of a cabinet On entry his temperature was 101.6° F There was moderate cervical and axillary adenopathy and the tip of the spleen was palpable The hemoglobin was 11 gm, leukocytes 4300 per cubic millimeter, with 20 per cent polymorphonuclear neutrophils, 69 per cent lymphocytes, 2 per cent monocytes, 8 per cent eosinophils and 1 per cent basophils. A blood culture failed to reveal the presence of *Brucella* During the first eleven days the patient received sulfadiazine, with a blood level of free sulfadiazine being maintained between 15.6 and 18.8 mg per 100 cc He developed a maculopapular skin eruption and leukopenia and neutropenia, which abated when treatment with sulfadiazine was omitted In addition, he was given four treatments with artificially induced fever at 105° F for four hours He recovered completely, and left the hospital fourteen days after entry

It was learned that this child ingested raw milk obtained from a local dairy One other case of brucellosis was traced to this source

### TREATMENT OF BRUCELLOSIS

There are two major factors which must be taken into consideration in evaluating any specific agent for the treatment of brucellosis, as pointed out so well by Carpenter and Boak<sup>63</sup> First, brucellosis is a disease having spontaneous remissions no matter what treatment is prescribed The course of the initial febrile attack may last for a few days up to several weeks As we have emphasized, brucellosis at times may be a very mild disease, particularly in those infections due to *Brucella abortus* It is known that rest in bed will alleviate the symptoms and the temperature will drop to normal, although the bacteremia may persist The average duration of an attack of brucellosis is about three months<sup>63</sup> A second factor, important in the interpretation of therapeutic results, is related to the accuracy of the diagnosis A review of the literature would indicate that in many instances there exists some doubt concerning the correct diagnosis With the foregoing facts in mind, we have attempted to evaluate the results of specific therapy for brucellosis

Chemotherapy.—Various chemotherapeutic agents have been tried in brucellosis and include methylene blue, mercurochrome, acriflavine,

methyl violet, metaphen, neoarsphenamine, neosalvarsan and, more recently, atabrine. There is no satisfactory evidence that these compounds are of specific value.

Of late, much interest has been attached to the therapeutic effectiveness of the *sulfonamides*. Here again, confusion exists because these compounds have been used in some patients where there is every right to question the diagnosis of brucellosis. There appears to be little doubt that all the more commonly used sulfonamides inhibit the *in vitro* growth of the three species of *Brucella*, and also offer some degree of protection, at least, to experimentally infected animals.<sup>64 65 66, 67</sup> We have observed *in vitro* that sulfadiazine will readily inhibit the growth of *Brucella* in therapeutic concentrations of the drug. This is particularly applicable to strains of *Brucella abortus*, which are more meticulous in their growth requirements than *suis* or *melitensis* strains.

We are convinced from our own experience that the sulfonamides are effective in the treatment of human infections, although Urschel<sup>68</sup> in a review of the literature in English expresses some doubt about sulfonamide therapy. But if one excludes most of the chronic cases treated, and centers attention on those instances where the disease has been proved to exist beyond any reason for doubt, one is impressed by the value of the sulfonamides. We have the impression that the sulfonamides are most effective in acute infections due to *Brucella abortus*, and in those patients who have a good immune response as reflected in the agglutinin titer. We agree with the majority of clinicians that the sulfonamides are of little or no value in the chronic ambulatory patient not having a demonstrable bacteremia. Although we have experienced satisfactory therapeutic results in patients having chronic brucellosis, the individuals selected for treatment were febrile, showing evidence of an active disease process being present. We cannot escape the conclusion that failure with the sulfonamides in chronic cases may be due to a mistaken diagnosis or the use of inadequate doses over too short a period. We have not treated a single ambulatory patient with sulfonamide. In the cases selected, the patients have been febrile, and have required hospital and bed care as a part of their treatment. As far as could be determined, all the patients were suffering from infections due to *Brucella abortus*. Wise<sup>69</sup> has indicated that sulfonamide therapy in adequate doses will not eradicate a bacteremia due to *Brucella suis*. We have some confirmatory evidence for this observation in that a patient with an acute brucellosis due to the *suis* species improved considerably during a course of sulfonamide treatment but the bacteremia persisted during the immediate afebrile, convalescent period.

At the University Hospitals, the sulfonamides have been administered to eight of ten patients having a bacteremia due to *Brucella abortus*. Of the group of eight patients, five had the chronic form of the

children under twelve years of age The essential clinical features in one of these children are as follows

CASE III—A 6 year old white male was seen with Dr Ralph Platou on the Pediatric Service The child had always enjoyed good health until approximately four months before entry when he developed chickenpox Following this he continued to complain of marked fatigue, and he became more and more listless He had a daily temperature elevation of 102° to 104° F About three weeks before admission he was seen by Dr Platou who suspected brucellosis because of a palpable spleen as the only localizing physical abnormality Blood sent to the Laboratories of the Minnesota State Department of Health revealed agglutinins for *Brucella abortus* present in a titer of 1 to 640, and a pure culture of *Brucella abortus* was isolated from his blood He was given sulfadiazine over a period of ten days in doses which established a blood level of free sulfadiazine of 11.5 mg per 100 cc

Because improvement was slow, it was decided to admit the patient to the hospital, continue with sulfadiazine therapy, and, in addition, institute treatment with artificial fever by means of a cabinet. On entry his temperature was 101.6° F There was moderate cervical and axillary adenopathy and the tip of the spleen was palpable The hemoglobin was 11 gm, leukocytes 4300 per cubic millimeter, with 20 per cent polymorphonuclear neutrophils, 69 per cent lymphocytes, 2 per cent monocytes, 8 per cent eosinophils and 1 per cent basophils. A blood culture failed to reveal the presence of *Brucella* During the first eleven days the patient received sulfadiazine, with a blood level of free sulfadiazine being maintained between 15.6 and 18.8 mg per 100 cc He developed a maculopapular skin eruption and leukopenia and neutropenia, which abated when treatment with sulfadiazine was omitted In addition, he was given four treatments with artificially induced fever at 105° F for four hours He recovered completely, and left the hospital fourteen days after entry

It was learned that this child ingested raw milk obtained from a local dairy One other case of brucellosis was traced to this source

#### TREATMENT OF BRUCELOSIS

There are two major factors which must be taken into consideration in evaluating any specific agent for the treatment of brucellosis, as pointed out so well by Carpenter and Boak<sup>68</sup> First, brucellosis is a disease having spontaneous remissions no matter what treatment is prescribed The course of the initial febrile attack may last for a few days up to several weeks As we have emphasized, brucellosis at times may be a very mild disease, particularly in those infections due to *Brucella abortus* It is known that rest in bed will alleviate the symptoms and the temperature will drop to normal, although the bacteremia may persist The average duration of an attack of brucellosis is about three months<sup>69</sup> A second factor, important in the interpretation of therapeutic results, is related to the accuracy of the diagnosis A review of the literature would indicate that in many instances there exists some doubt concerning the correct diagnosis With the foregoing facts in mind, we have attempted to evaluate the results of specific therapy for brucellosis

Chemotherapy—Various chemotherapeutic agents have been tried in brucellosis and include methylene blue, mercurochrome, acriflavine,

methyl violet, metaphen, neoarsphenamine, neosalvarsan and, more recently, atabrine. There is no satisfactory evidence that these compounds are of specific value.

Of late, much interest has been attached to the therapeutic effectiveness of the *sulfonamides*. Here again, confusion exists because these compounds have been used in some patients where there is every right to question the diagnosis of brucellosis. There appears to be little doubt that all the more commonly used sulfonamides inhibit the *in vitro* growth of the three species of *Brucella*, and also offer some degree of protection, at least, to experimentally infected animals.<sup>64 65 66, 67</sup> We have observed *in vitro* that sulfadiazine will readily inhibit the growth of *Brucella* in therapeutic concentrations of the drug. This is particularly applicable to strains of *Brucella abortus*, which are more meticulous in their growth requirements than *sus* or *melitensis* strains.

We are convinced from our own experience that the sulfonamides are effective in the treatment of human infections, although Urschel<sup>68</sup> in a review of the literature in English expresses some doubt about sulfonamide therapy. But if one excludes most of the chronic cases treated, and centers attention on those instances where the disease has been proved to exist beyond any reason for doubt, one is impressed by the value of the sulfonamides. We have the impression that the sulfonamides are most effective in acute infections due to *Brucella abortus*, and in those patients who have a good immune response as reflected in the agglutinin titer. We agree with the majority of clinicians that the sulfonamides are of little or no value in the chronic ambulatory patient not having a demonstrable bacteremia. Although we have experienced satisfactory therapeutic results in patients having chronic brucellosis, the individuals selected for treatment were febrile, showing evidence of an active disease process being present. We cannot escape the conclusion that failure with the sulfonamides in chronic cases may be due to a mistaken diagnosis or the use of inadequate doses over too short a period. We have not treated a single ambulatory patient with sulfonamide. In the cases selected, the patients have been febrile, and have required hospital and bed care as a part of their treatment. As far as could be determined, all the patients were suffering from infections due to *Brucella abortus*. Wise<sup>69</sup> has indicated that sulfonamide therapy in adequate doses will not eradicate a bacteremia due to *Brucella sus*. We have some confirmatory evidence for this observation in that a patient with an acute brucellosis due to the *sus* species improved considerably during a course of sulfonamide treatment but the bacteremia persisted during the immediate afebrile, convalescent period.

At the University Hospitals, the sulfonamides have been administered to eight of ten patients having a bacteremia due to *Brucella abortus*. Of the group of eight patients, five had the chronic form of the

disease, and three the acute form. One patient with endocarditis due to *Brucella* failed to respond to either sulfanilamide or sulfathiazole. Of the remaining seven patients, it was necessary to discontinue sulfonamide therapy in two individuals because of toxic reactions, and artificial fever therapy was instituted. Both of these patients recovered completely and have remained in good health. Of the other five patients, one had a temporary relapse following sulfonamide therapy, but recovered completely after a second course of sulfonamide treatment. With the exception of this one patient, all have remained in good health for one or more years following treatment. *The bacteriemia was eradicated in every instance coincident with the use of a sulfonamide except in the patient with brucella endocarditis.*

Eighteen patients without a demonstrable bacteriemia, but for whom it is believed satisfactory evidence was at hand to establish the disease, were treated with the sulfonamides. There were five acutely ill patients, and all recovered completely and have remained well for more than a year. Of the thirteen patients with the chronic form of the disease, nine have had a complete remission of symptoms for one or more years. There were four who failed to respond satisfactorily. One of these four patients was unable to tolerate sulfonamide treatment, and recovered following artificial fever therapy. A second patient was given two courses of sulfonamide therapy without improvement, and then received artificial fever therapy with but slight temporary improvement. A third patient had a good temporary response, but then relapsed. A fourth was given a short course with a sulfonamide, and then artificial fever therapy with a satisfactory recovery.

In the initial attempts to evaluate sulfonamide therapy, sulfanilamide, sulfapyridine or sulfathiazole was employed. During the last two years we have used sulfadiazine and, more recently, sulfamerazine. It is our policy to hospitalize patients for treatment, and continue therapy for two to three weeks. Blood concentrations of sulfadiazine or sulfamerazine are maintained around 10 mg per 100 cc. Four grams of sulfadiazine are given as an initial dose, and then one gram every four to six hours. Each adult patient is given 4 gm of soda bicarbonate four times a day in order to insure an alkaline urine. Fluids are administered so that the daily urinary output is from 1000 to 1500 cc. With sulfamerazine, slightly smaller doses are given and at less frequent intervals.

There is no reason to believe that penicillin will prove effective in the routine treatment of patients having brucellosis. Preliminary in vitro studies indicate that strains of *Brucella* are quite resistant to the action of penicillin.

**Vaccine Therapy**—For the most part, *Brucella* vaccine has been reserved for the treatment of chronic cases of brucellosis. There is no unanimity of opinion that such a vaccine is specific for brucellosis. Carpenter and Boak<sup>63</sup> conclude that a specific effect is lacking and favorable results are due to nonspecific systemic reactions. Evidence

in favor of this view is that satisfactory results have followed the intravenous injection of killed typhoid-paratyphoid organisms<sup>70</sup> Harris<sup>2</sup> is a firm advocate of the employment of heat-killed *Brucella* vaccine. There is also a difference of opinion as to whether a clinician should use a mixed *Brucella* vaccine, or the vaccine obtained from a single species of *Brucella*. Furthermore, some advocate the intramuscular route of injection, others the intradermal administration, and others warn against its administration by the intravenous route.

Apparently there is some confusion as to how the specific action of *Brucella* vaccine operates. Some maintain that immunity is established as reflected in the opsonocytophagic test. Others feel that the important feature is desensitization of the patient to the products of the *Brucella*. It would appear that both phenomena are present, that is an increase in the antibody response, and an increase in the tolerance of the patient to the vaccine. In interpreting these factors it should be mentioned that immunologists have expressed considerable doubt as to whether any vaccine has a specific therapeutic value in any chronic infectious disease.

As a result of observation in our own clinic, we are not too optimistic concerning the therapeutic value of *Brucella* vaccine. We do not advocate its use in the acute stages of the disease, and in the undoubted chronic case we first prefer a therapeutic trial with the sulfonamides. Failing in this, our second choice is artificial fever therapy which will be discussed shortly. Where *Brucella* vaccine has been used, we have employed a heat-killed vaccine prepared from *Brucella abortus*. The vaccine is given every five days intramuscularly in increasing doses for five or six times, though in several instances we have continued treatment much longer than this. The object is to provoke a moderate systemic reaction with each injection. The dose of the initial injection depends upon the sensitivity of the individual to the vaccine as measured by an intradermal test.

**Brucellin**—Huddleson and his associates<sup>1</sup> have advocated the intramuscular use of a broth filtrate prepared from the three species of *Brucella*. According to these workers, the immunologic basis for using brucellin is a state of sensitivity of the patient to the material, its injection produces "a systemic allergic reaction which in turn is accompanied by a neutrophilic leucocytosis and increase in immune opsonins." Furthermore, brucellin does not affect the course of the disease in a patient who is not sensitive. We have had no experience with brucellin but we would not consider brucellin the agent of first choice in an acutely ill patient having bacteremia, even though he was sensitive to the material. It is difficult to state whether brucellin is superior to vaccine in the treatment of chronic brucellosis.

**Immune Serum**—The use of specific antisera prepared from immunizing animals has not been accompanied by very encouraging results.<sup>63</sup> Human immune serum appears to be of some value.<sup>71, 72</sup> We



have not had the opportunity of utilizing any antibrucella serum. Further evaluation of a concentrated antibrucella serum should be encouraged. There is evidence that, in cattle recovering from *Brucella abortus* infection, bactericidins may be demonstrated in the serum in the absence of an appreciable titer of agglutinins.<sup>73</sup>

**Fever Therapy**—Physically induced hyperpyrexia has been advocated by Prickman and his associates<sup>74, 75</sup> in the treatment of selected groups of patients with brucellosis. They advise such therapy for patients with the acute form of the disease, and individuals having bone lesions, such as spondylitis. We have treated five patients having chronic brucellosis in the Kettering hypertherm at the University Hospitals after failure with sulfonamide therapy. Satisfactory results were obtained in four of the five patients. This type of therapy merits further consideration.

### SUMMARY AND CONCLUSIONS

Brucellosis is a disease with protean clinical manifestations. The acute stage of the disease may be so mild that it may be overlooked, or the more serious infections may be incorrectly diagnosed. The accurate diagnosis of chronic brucellosis constitutes a major problem in clinical medicine. A precise diagnosis depends upon a correlation of epidemiologic data, that is, a history of exposure to the organisms, certain localizing physical signs, and a careful interpretation of laboratory data. A reliance upon inadequate laboratory findings is often the cause of incorrect diagnoses. For practical purposes, the most dependable laboratory data include a relative or absolute lymphocytosis in the peripheral blood, the presence of agglutinins for *Brucella*, and the isolation of *Brucella* from the tissues or body fluids. The intradermal test with *Brucella* antigen is often more confusing than helpful. When other clinical and laboratory evidence for the disease is present, the skin test may be of aid. A more satisfactory therapeutic agent is needed for brucellosis. At the University Hospitals, the sulfonamides have proved to be definitely beneficial in the therapy of acute and active chronic infections due to *Brucella abortus*. The therapeutic results with *Brucella* vaccine must be carefully interpreted. This also applies to brucellin. The use of potent antiserum should be encouraged and evaluated further. Physically induced hyperpyrexia may be beneficial in selected patients.

### BIBLIOGRAPHY

- 1 Huddleson, I. F. *Brucellosis in Man and Animals*. New York, The Commonwealth Fund, 1939.
- 2 Harris, H. J. *Brucellosis*. New York, Paul B. Hoeber, Inc., 1941.
- 3 Terry, L. L. *Texas State J. Med.*, 37:359 (Sept.) 1941.
- 4 Borts, I. H. *et al.* *J.A.M.A.*, 121:319 (Jan. 30) 1943.
- 5 Fitch, C. P. and Boyd, W. L. *Bull.* 348, University of Minnesota Agricultural Experiment Station, June, 1940.
- 6 Carpenter, C. M. and Boak, R. A. *J. Bact.*, 33:40 (Jan.) 1937.

- Morales-Otero P. Puerto Rico J. Pub. Health & Trop. Med., 63, 1930
- Hardy, A. V., Hudson M. G. and Jordan, C. F. J. Infect. Dis., 45:271 1929
- Strong, R. Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases. Philadelphia, Blakiston Co., 1942, Vol. 1 Chap. XXI p. 739
- Neighbors, D. Texas State J. Med., 37:353 (Sept.) 1941
- Meyer, K. F. and Eddie, B. J. Infect. Dis., 68:24 1941
- Hardy A. V. et al. National Institute of Health Bulletin No. 158, 1931
- Spink, W. W. and Hoffbauer F. W. Journal Lancet, 61:13 (Jan.) 1941
- Simpson, W. M. Ann. Int. Med., 4:238 1930
- Jordan C. F. J. Infect. Dis., 48:526 (June) 1931
- Dooley P. Arch. Int. Med., 50:373, 1932
- Johns, E. P., Campbell, F. J. H. and Tennant, C. S. Canad. M. A. J., 27:490 (Nov.) 1932
- Beattie, C. P. and Rice, R. M. J.A.M.A., 102:1670 (May 18) 1934
- Boris, I. H. et al. J.A.M.A., 121:319 (Jan. 30) 1943
- Shaw E. A. Report of the Commission for the Investigation of Mediterranean Fever Part IV pp. 8-15 1906.
- Evans, A. C. J.A.M.A., 103:665 (Sept. 1) 1934
- Robinson, F. H. and Evans, A. C. J.A.M.A., 113:201 (July 15) 1939
- Forbus, W. D. Reaction to Injury. Baltimore, Williams and Wilkins Co., 1943, p. 642.
- Parsons, P. B. and Poston, M. A. South. Med. J., 32:7 (Jan.) 1939
- Wise, N. B. and Poston, M. A. J.A.M.A., 115:1976 (Dec. 7) 1940
- Poston, M. A. and Parson, P. B. J. Infect. Dis., 66:86 (Jan.-Feb.) 1940
- Spink, W. W. and Nelson, A. A. Ann. Int. Med., 13:721 (Oct.) 1939
- Spink, W. W., Titrud L. A. and Kabler P. Am. J. M. Sc., 203:797 (June) 1942
- Dietrich H. and Bonyng, C. W. J. Pediatr., 1:46 1932
- Green, J. Arch. Ophthalmol., 21:51 (Jan.) 1939
- Burky E. E., Thompson, R. R. and Zepp H. Am. J. Ophthalmol., 22:1210 (Nov.) 1939
- Poston, M. A. and Menefee, E. E., Jr. New England J. Med., 219:796 (Nov. 17) 1938.
- Johnson, R. M. Am. J. M. Sc., 189:483 1935
- Macdonald, R. H. J. Thoracic Surg., 9:92 (Oct.) 1939
- Bogart, F. B. South. Med. J., 29:1 (Jan.) 1936
- Mettner S. R. and Kerr W. J. Arch. Int. Med., 54:702 (Nov.) 1934
- Chaikin, N. W. and Schwimmer D. Rev. Gastroenterol., 10:130 (March-April) 1943
- Zaus, E. A. and Espey H. S. Illinois M. J., 82:144 (Aug.) 1942.
- Carpenter C. M. and Book, R. J.A.M.A., 96:1212 (April 11) 1931
- Janbon M. and Caderas de Kerlau, J. Presse Medicale, 47:453 1939
- Calder R. M. South. Med. J., 32:451 (May) 1939
- Bloomfield, A. L. Am. Rev. Tuberc., 45:741 (June) 1942
- Rubenstein, A. D. and Shaw C. I. New England J. Med., 231:111 (July 27) 1944
- De Jong R. N. J. Nerv. & Ment. Dis., 83:430 1936.
- Green, M. E. and Freyberg R. H. Am. J. M. Sc., 201:495 (April) 1941
- Bishop W. A., Jr. J. Bone & Joint Surg., 21:665 (July) 1939,
- Feldman W. H. and Olson, C., Jr. Arch. Path., 16:195 (Aug.) 1943,
- Foshay L. Am. J. Clin. Path., 10:176 (Feb.) 1940
- Agnew S. The Use of the Opsonocytaphag Test in the Study of Brucellosis. A thesis submitted to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Master of Science, May 1942

- 50 Huddleson, I F, Johnson, H W and Hamann, E. E Am J Pub Health, 23:917, 1933
- 51 Jersild, M J Infect. Dis, 68 16, 1941
- 52 Calder, R M., Steen, C and Baker, L J A.M.A., 112 1893 (May 13) 1939
- 53 Castaneda, M R., Tovar, R and Velez, R. J Infect. Dis, 70:97 (March-April) 1942
- 54 Taylor, R. M *et al* Bull Health Organization of the League of Nations, 7 503 (June) 1938
- 55 Kirby, W M M and Rantz, L A J Lab & Clin Med., 27 1244 (July) 1942.
- 56 Menefee, E E., Jr and Poston, M A Am J M Sc, 197 646 (May) 1939
- 57 Wise, B and Craig, H W J Infect. Dis., 70 147 (March-April) 1942
- 58 Wise, B Am J M Sc., 200 520 (Oct.) 1940
- 59 Morales-Otero, P and Gonzalez, L M Proc Soc Exp Biol & Med., 38 703, 1938
- 60 Heathman, L S J Infect. Dis, 55 243 (Nov-Dec) 1934
- 61 Smith, D T and Poston, M A Trans Am Clin & Climatolog Assoc., 1937
- 62 McIntire, F T Texas State J Med, 37 355 (Sept.) 1941
- 63 Carpenter, C M and Boak, R A Medicine, 15.103 (Feb) 1936
- 64 Wilson, G S and Maier, I Brit. M J., 1 8 (Jan 7) 1939
- 65 Morales-Otero, P and Pomales-Lebrón, A Proc. Soc Exper Biol & Med, 45 512, 1940
- 66 Chinn, B D Infect. Dis., 18 78 (Jan.-Feb) 1939
- 67 Wise, B J Pharm & Exper Therap, 76 156 (Oct.) 1942
- 68 Urschel, D L Indiana State M A J, 37 57 (Feb) 1944
- 69 Wise, B Arch Int Med., 72 346 (Sept.) 1943
- 70 Ervin, C E and Hunt, H F J A.M.A., 109 1966 (Dec 11) 1937
- 71 Poston, M A and Smith, D T New England J Med., 215 369 (Aug 27) 1936
- 72 Poston, M A and Menefee, E E., Jr New England J Med, 219 796 (Nov 17) 1938
- 73 Irwin, M R and Ferguson, L C Proc Soc Exp Biol & Med, 38 451 (May) 1938
- 74 Prickman, L E., Bennett, R L and Krusen, F H Proc Staff Meetings Mayo Clinic, 13 321 (May 25) 1938
- 75 Phalen, G S., Prickman, L E and Krusen, F H J.A.M.A., 118 859 (March 14) 1942

# CIRRHOSIS OF THE LIVER WITH PARTICULAR REFERENCE TO CORRELATION OF COMPOSITE LIVER FUNCTION STUDIES WITH LIVER BIOPSY

FREDERICK W. HOFFBAUER, M.S., M.D.\*; GERALD T. EVANS, M.D.,  
PH.D.†, AND CECIL J. WATSON, M.D., PH.D., F.A.C.P.‡

IN MANY instances cirrhosis of the liver presents no great problem in differential diagnosis but often enough its manifestations are perplexing, and it is in this group that the clinician needs all available aids in the solution of the problem. A study of hepatic disease in general resolves itself into two main divisions: (1) recognition of hepatic disturbances when outspoken clinical signs are lacking and (2) recognition of the cause or type of hepatic disease when clinical signs such as jaundice are evident.

## THE COMPOSITE LIVER FUNCTION STUDY

The large number of procedures which have been proposed to evaluate the functional status of the liver clearly indicates that no single procedure is in itself entirely reliable or diagnostic. It would probably be unduly optimistic to anticipate a subsequent development of any single method which would regularly reveal the composite functional status of the liver. The innumerable functions of this organ and the variable way that they may be impaired would appear to preclude the possibility of a "miracle" test. The clinician must therefore choose from the array of tests available those best suited to a given case. Thus in the presence of jaundice, the bromsulfalein test has relatively little value, while it is often of the greatest help in seeking for evidence of liver disease in the nonjaundiced subject. Certain tests, such as Hanger's cephalin-cholesterol flocculation, are actually not methods of measuring liver function, but rather, of liver cell injury or irritation.

For the past several years we have been interested in correlating composite studies of liver function with the histology of the liver. In the discussion which ensues, only cases of proven histologic diagnosis

---

From the Department of Medicine and the Laboratory Service, University of Minnesota Hospital, Minneapolis, Minnesota. Aided by grants from Hormel Research Foundation and the Research Fund of the Graduate School, University of Minnesota. Presented in part before the annual meeting of the Central Society for Clinical Research, Chicago, Nov. 3 and 4, 1944.

Assistant Professor of Medicine, Department of Medicine, University of Minnesota Medical School.

†Associate Professor of Medicine, Department of Medicine, University of Minnesota Medical School. Director of the Hospital Laboratory Service, University of Minnesota Hospitals, Minneapolis, Minnesota.

‡Professor of Medicine, Department of Medicine, University of Minnesota Medical School.

are included. This has depended in part upon needle biopsy, as described in the following, and in part upon necropsy material. For purposes of comparison and easier evaluation in the present study the results of a number of procedures have been recorded graphically in the form of a liver function "profile" or composite record which has been referred to in previous communications<sup>1, 2</sup>

In the nonjaundiced subject, the following procedures have been included: quantitative serum bilirubin, hippuric acid synthesis, fractional serum protein, cephalin-cholesterol flocculation test, bromsulfalein excretion test, and the quantitative urine urobilinogen test. In the jaundiced patient, this same group of tests, with the exception of the bromsulfalein, is employed. In addition, the serum cholesterol and alkaline phosphatase, the prothrombin time before and after vitamin K administration, and the feces urobilinogen are determined when jaundice is present.

In the majority of these tests, the technics used are those in common practice in clinical laboratories. A few modifications of certain procedures have proved of value. For the quantitative determination of the serum bilirubin a slight modification<sup>3</sup> of Malloy and Evelyn's method<sup>4</sup> has been used. After the addition of the van den Bergh reagent, readings are taken at one minute and again at fifteen minutes representing the prompt direct and the delayed direct reacting bilirubins respectively. The total and the indirect reacting bilirubins are then determined in the usual way. Characteristic values for a case of obstructive jaundice would be recorded as follows: serum bilirubin in milligrams per 100 cc  $1' = 20$ ,  $15' = 23$ , total = 28.

In the determination of the ability of the liver to conjugate hippuric acid after sodium benzoate, the intravenous method of Quick<sup>5</sup> has been employed. In the presence of renal insufficiency hippuric acid excretion is delayed. Machella, Helm and Chornock<sup>6</sup> have shown that the outcome of the test is in a measure dependent upon adequate urine flow. To evaluate the renal function simultaneously we have simply injected 1 cc of phenolsulfonphthalein (6 mg phenolsulfonphthalein dye) through the same needle after giving the sodium benzoate. The urine specimen is collected at the end of sixty minutes and an aliquot is used to determine the dye excretion, the balance being employed for the determination of the hippuric acid. An excretion of less than 35 per cent of the phenolsulfonphthalein dye in the one-hour sample casts doubt on the reliability of a low hippuric acid excretion as a measure of hepatic cell function. Conjugation may have occurred in the liver but the excretion of the resultant product is retarded by poor renal function. This simple procedure evaluates renal function at the time that such knowledge is most desirable, viz., during the actual hour the hippuric acid test is being conducted.

The urinary and fecal excretion of urobilinogen has been determined by the quantitative method previously described by Watson.<sup>7</sup>

For the cephalin cholesterol flocculation test of Hanger<sup>8</sup> a commercial antigen\* has been found to be satisfactory

The serum alkaline phosphatase has been determined by the procedure described by King and Armstrong<sup>9</sup> The values are expressed in terms of King-Armstrong units in the figures accompanying the following case reports

The method of Quick<sup>10</sup> has been employed for the prothrombin time determination In the event of an elevated initial value, the determination has been repeated twenty-four hours after the parenteral administration of 1 mg of synthetic vitamin K. The second value has been termed "prothrombin response" on the graphic record form (see Fig 62) The value of such a procedure as an aid in the differential diagnosis of jaundice has been pointed to by Allen and Julian,<sup>11</sup> Lord and Andrus,<sup>12</sup> Olwin<sup>13</sup> and Kark and Souter<sup>14</sup>

The use of a composite liver function study, with the results depicted in graphic form, has proved of considerable help in the analysis of hepatic disorders In the charts that accompany the cases cited, the values departing above the midhorizontal line indicate in general a diminishing liver function, while those departing below the line indicate either normal liver function or, in some instances, simple biliary obstruction without disturbance of function. By connecting the various values plotted, one may obtain a "profile" of liver function for any given case. Eventually it is hoped that the accumulation of sufficient data of this type correlated with the histologic appearance of the liver will then permit diagnostic deductions from the future graphic forms alone.

#### NEEDLE BIOPSY OF THE LIVER

Since 1942 needle biopsy of the liver has been attempted in eighty-five cases of hepatic disease occurring on the Medical Service of the University of Minnesota Hospitals. The method has often permitted accurate diagnosis in instances where laboratory and clinical findings were inconclusive.

Aspiration of the liver to obtain material for histologic study is not a new procedure. So far as can be determined it was first employed by Lucatello,<sup>15</sup> who however, did not employ fixation or staining, so that the examination of the tissue obtained permitted little in the way of an accurate diagnosis Twelve years after this initial report, Schupfer recorded his observations on aspiration biopsy of the liver<sup>16</sup> He employed modern methods of tissue fixation and staining One of the most extensive series of needle biopsies of the liver was that reported by Bingel<sup>17</sup> in 1923 This account records the use of the method in 100 cases Most of the same cases appear to be included again in a subsequent series of 140 cases reported by Olivet<sup>18</sup> in 1926 Two fatalities due to hemorrhage and one due to peritonitis are listed in this series.

Difco Company Detroit, Michigan.

The earlier reports of aspiration liver biopsy are reviewed in Frola's monograph published in 1935<sup>19</sup> This investigator analyzed sixty-six of his own cases in which liver tissue was obtained by means of suction applied to a small (0.5 mm) bore needle inserted into the liver The material obtained, if one may judge from Frola's published photomicrographs, consisted only of fragments of liver tissue and blood cells The use of a fine-bore needle, while undoubtedly somewhat safer, yields so little tissue that its value is very limited

A most important advance in the use of liver biopsy arose from the studies of two Danish investigators, Iverson and Roholm<sup>20</sup> Their method consisted of an aspiration technic through a posterior-lateral approach to the liver, the site of entrance being the ninth intercostal space in the right posterior axillary line Infiltration of a local anesthetic agent is made at this site and the skin punctured with a knife A needle 18 cm long and 2 mm in width is inserted through the pleura and diaphragm and carried into the liver The pointed obturator is then removed from the needle leaving the serrated cutting edge of the needle embedded in the posterior liver surface Suction is applied by means of a Record syringe attached to the needle hub as the needle is advanced several centimeters into the liver This usually results in removal of a small plug of tissue which is drawn up into the needle along with a few cubic centimeters of blood In England, Dible, McMichael and Sherlock<sup>21</sup> describe satisfactory results with the method of Iverson and Roholm in studies of cases of epidemic, postarsphenamine and homologous serum jaundice as well as in cirrhosis A few untoward results were encountered by this group as well as by the originators of the method These were in the main hemorrhage, the statement is made that the method should be reserved for cases justifying the slight risk entailed

Baron, in 1939,<sup>22</sup> reported forty-eight aspiration biopsies of the liver by an anterior approach, entering the liver below the rib margin A 13-gauge needle 9 cm long was inserted into the liver and material was then obtained by suction A fatal hemorrhage occurred in one of the cases in Baron's series The anterior approach was also employed by Chiray, Fiessinger and Roux in a report of forty-one cases published in 1941<sup>23</sup> These investigators recommended a trocar 6 cm in length and 1.5 mm in width After local infiltration anesthesia, the trocar was passed through the anterior abdominal wall beneath the costal margin and into the liver for a distance of 2 cm Suction was then applied and the needle advanced for a depth of another 1 cm Failure to secure tissue was reported in nine instances No untoward result occurred in this series because, as the authors believe, the penetration to a depth of only 3 cm avoids the large vessels of the liver They recommend that the procedure be reserved for enlarged and easily palpable livers, on the basis of our experience, using a similar method of approach to the liver, we concur entirely with this recommendation

Needle biopsy of the liver using the Vim-Silverman needle was described by Tripoli and Fader in 1941<sup>24</sup> This needle\* (Fig 61) is an ingenious device primarily intended for tumor biopsy<sup>25</sup> By inserting this needle into the liver anteriorly beneath the right costal margin Tripoli and Fader obtained satisfactory tissue specimens in a series of cases Local anesthesia was employed, the site of insertion of the needle being at the lateral edge of the right rectus muscle, below the costal margin

In the present series of cases we have employed the Vim-Silverman needle in all instances in which liver biopsy has been done. The pro-

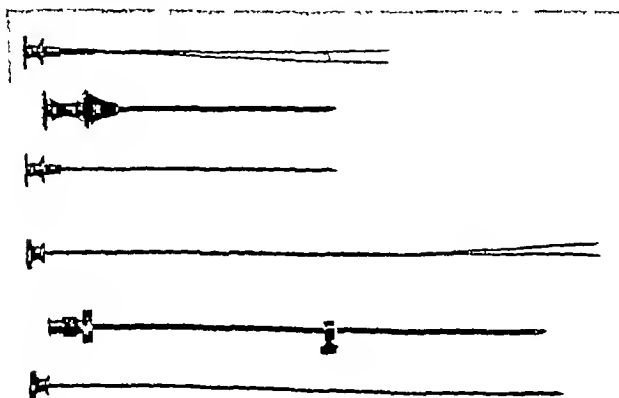


Fig 61—The upper three pieces depict the ordinary Vim-Silverman biopsy needle (MacGregor Instrument Co) The lower set represents a longer needle based on the same principle which has been devised by us to obtain needle biopsy of the liver during peritoneoscopy

cedure is carried out at the bedside except when done at the time of peritoneoscopy When necessary, a preliminary injection of morphine is given to the patient to allay apprehension. The right upper quadrant of the abdomen is prepared with an antiseptic solution and the area draped Procaine solution is infiltrated at the site selected for the needle insertion Infiltration is carried down to the parietal peritoneal surface If some of the anesthetic agent can be injected just at the peritoneum, the procedure is made relatively painless. The infiltrating needle, a 3-inch 22-gauge one, is finally advanced beyond the peritoneum and into the liver Entrance into the liver is noted by movement of the

\* MacGregor Instrument Co., Needham, Mass.



needle coincident with respiration. Suction is applied briefly to be certain one has not encountered an abscess or an excessively vascular area. This having been ascertained to satisfaction, the small bore needle is withdrawn. A small skin incision, 3 mm in length, is then made to facilitate passage of the Vim-Silverman needle. The latter is directed through the anesthetized tract and inserted a short distance into the liver substance. The obturator is then withdrawn and the inner-split needle is inserted into the outer one. The inner needle is then advanced its full length so that the two halves of the needle trap a core of liver tissue. Next the outer needle is advanced, moving over the inner-split needle so that the two halves are compressed. In this manner the piece of tissue is secured between the two prongs. One rotation of the outer needle, holding the inner one stationary, serves to cut the tissue core at its base. The two needles are then withdrawn together. The specimen will vary in length from 1 to 2.5 cm. It is about 0.8 mm in width. Fixation of the plug in 5 cc of 10 per cent formalin for twelve to twenty-four hours is recommended.

Following such a procedure the patient may experience mild right upper quadrant discomfort for a few hours. We have limited the use of this method to hospital patients and require twenty-four hours of strict bed rest following the biopsy. It should be emphasized that the procedure is not without slight risk and that it should be reserved for cases in which the liver is definitely enlarged and the lower margin readily palpable at least 5 cm below the costal margin in the right midclavicular line. This limitation of course reduces the applicability of the method but also greatly reduces the risk. In the past two years sixty-five such biopsy attempts have been carried out at the bedside. In fifty instances, a piece of tissue sufficient for histologic examination has been obtained. Nine of the failures occurred in the first twenty attempts, before familiarity with the method had been gained.

Serious hemorrhage from the liver itself has not occurred. In one instance the needle was inserted too deeply into a thin left lobe and passing completely through it, undoubtedly damaged a large vessel beneath. An alarming intraperitoneal hemorrhage resulted, operation was performed as soon as the patient's condition was improved by transfusions. After the blood was evacuated from the peritoneal cavity, the surgeon found a large hematoma at the site of the damaged vessel. The area was left undisturbed and the abdomen was closed. The patient made a surprisingly uneventful recovery and exhibited no apparent after-effect. This case undoubtedly should not have been chosen since the liver was only very slightly enlarged, the left lobe being more easily palpable. Since this one misfortune we have made it a rule never to consider the procedure except in instances in which the liver is definitely enlarged.

The risk of bleeding from the liver surface itself is not great if the needle is prevented from making a linear tear in the parenchyma. The

danger of such a tear is one disadvantage of the methods requiring intercostal insertion of the biopsy needle. With the needle fixed between the ribs, movement of the liver coincident with respiration might result in a laceration of the capsule and parenchyma. This possibility has been commented upon by Baron.<sup>22</sup> We have watched the bleeding from the liver as a result of the biopsy with the Vim-Silverman needle when this has been done during laparotomy in the operating room. Not more than 5 to 10 cc of blood has been noted to escape before coagulation occurred. As a routine precaution, the bleeding time, clotting time and prothrombin time of each patient subjected to needle biopsy have been determined. The presence of any serious bleeding tendency is a contraindication. Likewise the presence of passive congestion of the liver or the presence of suspected hepatic abscesses or suppurative cholangitis is deemed a contraindication to needle biopsy. When the need for liver biopsy in the patient with a small or a normal sized liver has arisen, the procedure of peritoneoscopy has been the method of choice.

#### PERITONEOSCOPY IN THE DIFFERENTIAL DIAGNOSIS OF HEPATIC CIRRHOSIS

The advantages of peritoneoscopy for the diagnosis and study of disorders of the liver have been well described by Ruddock<sup>26</sup> and by Benedict.<sup>27</sup> This is a procedure that is best carried out in an operating room, although local anesthesia is quite adequate. The visualization of the liver afforded by the method often permits the diagnosis of hepatic cirrhosis. The Ruddock peritoneoscope is equipped with a forcep attachment intended for biopsy.

Biopsy of the liver when taken just beneath the capsule by means of these forceps, has one disadvantage, i.e. that of gaining a false concept of the amount of change throughout the liver, because of increased connective tissue or round cells just beneath the capsule. For this reason we have performed needle biopsy at the time of peritoneoscopy in twenty cases. The Vim-Silverman needle is not long enough to reach the liver surface through the anterior abdominal wall in the presence of the pneumoperitoneum necessary for peritoneoscopy. We have therefore simply increased the length of the needle to 18 cm as shown in Figure 61. This needle is inserted through a separately anesthetized area in the anterior abdominal wall below the right costal margin. With the liver in view through the peritoneoscope the operator can guide the needle into a desired site in the liver. This permits sampling of the liver to a greater depth than is possible by the forcep biopsy method.

#### ILLUSTRATIVE CASES

The following cases serve to emphasize some of the factors discussed in the preceding pages. In each the question of hepatic cirrhosis entered into the differential diagnosis at some point. The cases serve to illustrate the variable manner in which these different procedures have

aided in arriving at a correct diagnosis. There is no intention to imply that laboratory tests alone make a diagnosis for the clinician. When considered together with the history and the physical examination they do, however, permit an increased accuracy of diagnosis in hepatic disease. The addition of liver biopsy aids still further in the solution of some of the problems encountered.

CASE I—J S, a housewife aged 54 years, was referred to the hospital with the diagnosis of carcinoma of the pancreas and resultant common bile duct obstruction. Jaundice had been present for ten months, it was painless in its onset. Abdominal distention had been gradually increasing for four months prior to hospital entry. The patient complained of pruritus of moderate severity. During the period of jaundice the stools were light in color and the urine dark. Review of the patient's past history revealed little of note. She had had an episode of jaundice as a child, during an epidemic of infectious jaundice. No residual ill effects could be recalled.

Physical examination revealed a well nourished white woman. The degree of jaundice was marked, the skin exhibited a greenish yellow cast. Over the shoulders and upper chest, numerous "spider nevi" were present, of the type commonly seen in cases of hepatic cirrhosis. The abdomen was distended and free fluid was readily demonstrated. Edema of the ankles was present. Following diuresis induced by a mercurial, the decrease in ascites permitted palpation of a large firm liver extending 15 cm below the costal margin.

The results of the composite liver function study are depicted graphically in Figure 62. The degree of hyperbilirubinemia (Fig 62, SB) was marked. Of considerable interest was the complete exclusion of bile from the intestinal tract as evidenced by the practical absence of urobilinogen from the feces (Fig 62, FU). This was confirmed by repeated stool examinations. A value of feces urobilinogen below 5 mg per day is seen commonly in jaundice due to cancerous obstruction and infrequently in jaundice due to cirrhosis.<sup>28</sup> The lack of increase of the urine urobilinogen in this case (Fig 62, UU) does not necessarily reflect inadequate liver function. In the presence of complete biliary obstruction urobilinogen is not formed and consequently it cannot appear in the urine regardless of the state of the liver. As initially determined, this patient exhibited a marked deficiency of prothrombin (Fig 62, PT). Within twenty-four hours after a single injection of vitamin K this returned to normal (Fig 62, PR). This rapid response suggested adequate hepatic function in this particular respect. Taken by itself only, the prothrombin response lent support to the diagnosis of extrahepatic biliary obstruction. The value of the blood cholesterol (Fig 62, TC) was not high, as one usually anticipates in extrahepatic obstructive jaundice. The positive cephalin cholesterol reaction, the failure to synthesize any hippuric acid after sodium benzoate injection and the altered plasma protein values, all suggested parenchymal liver damage.

Further measures were resorted to in an effort to analyze the hepatic function. In view of the absence of the native urobilinogen in the urine, the patient was subjected to the stercobilin tolerance test.<sup>29</sup> In the twenty-four hours following the intravenous injection of 50 mg of crystalline stercobilin, 30 mg of urobilinogen appeared in the urine (Fig 62, ST). This constituted evidence of a markedly reduced functional capacity of the liver in this respect. It must be pointed out, however, that long-continued biliary stasis often affects liver function adversely, and we have observed similar results with the stercobilin tolerance test in some cases of neoplastic biliary obstruction, although in some instances the results are entirely normal. In contrast with the stercobilin tolerance test the galactose tolerance test in this case (Fig 62, G) was within normal limits. This

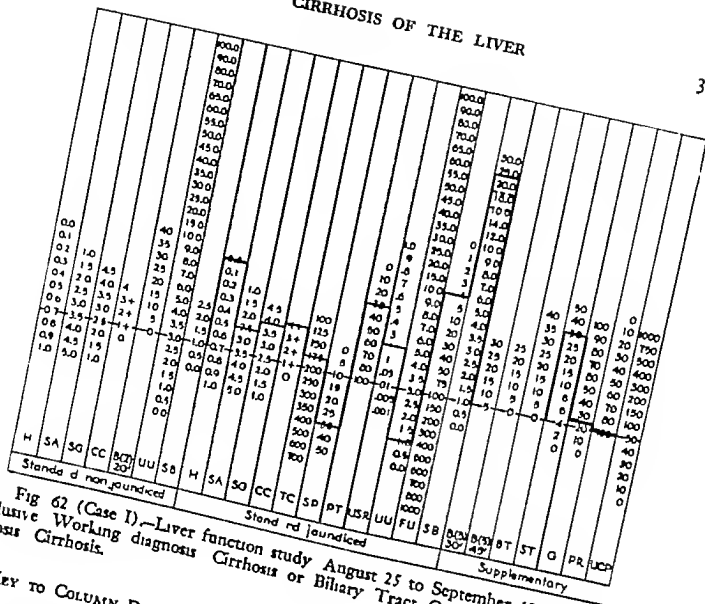


Fig 62 (Case I).—Liver function study August 25 to September 10, 1942 in Case I. Working diagnosis Cirrhosis or Biliary Tract Carcinoma. Final diagnosis Cirrhosis.

KEY TO COLUMN DESIGNATIONS IN THIS AND THE FOLLOWING LIVER FUNCTION STUDY CHARTS

- H Hippuric acid in gm., 1 hour urine specimen (177 gm Na benzoate i v)
- SA Serum albumin in gm per 100 cc
- SG Serum globulin in gm. per 100 cc.
- CC Cephalin cholesterol 0 to 4+
- B(2) Bromsulfalein, 2 mg per kilo., in per cent retained
- B(5) Bromsulfalein, 5 mg per kilo., in per cent retained
- SB Total serum bilirubin in mg per 100 cc. (lower broken line [when present])
- UU Urine urobilinogen in mg per 24 hours
- FU Feces urobilinogen in mg per 24 hours
- TC Total serum cholesterol in mg per 100 cc
- PT Prothrombin in per cent of normal
- BT Bilirubin tolerance, per cent retained 4 hours after 1 mg per kilo., i-v
- ST Stercobilin tolerance, mg (as urobilinogen) appearing in 24-hour urine after 50 mg
- G Mg galactose in blood 75 minutes after 0.5 gm per kilo., i-v
- PR Per cent response of prothrombin toward normal after 1 mg 2 methyl 14 naphthoquinone, i-v
- SP Serum phosphatase in units
- UCP Urine coproporphyrin in  $\gamma$  per 24 hours
- USR Urine-stool urobilinogen ratio

contrast at once reveals the striking difference in the way different functions may be affected in the same case

The photomicrograph from the needle biopsy is shown in Figure 63 Dr J S McCartney of the Department of Pathology reported as follows on this section

"This piece of tissue shows parts of at least 8 liver lobules, in two of which the central veins are recognized The liver cells are markedly pigmented There are many bile thrombi The portal tissues are greatly increased in extent with fibrous tissue There are large numbers of newly formed bile ducts in these spaces There is little or no leukocytic infiltration in any portal space

"Conclusion Cirrhosis of the liver with jaundice"

After establishment of the diagnosis, dietary therapy was promptly instituted The patient showed little or no improvement on a regimen of a high protein,

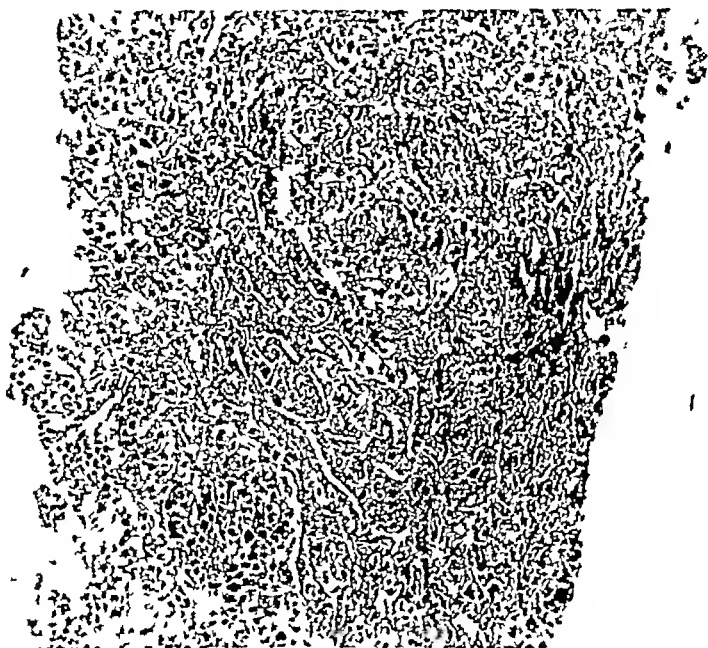


Fig 63 (Case I) —Photomicrograph from needle biopsy of the liver

high carbohydrate, low fat diet fortified with vitamin concentrates Choline hydrochloride, 1 gm daily, was administered for a period of one month without appreciable benefit Three months after discharge from the hospital, the patient expired Autopsy was not performed

In an analysis of this case, one may find clinical and laboratory evidence to support the diagnosis of extrahepatic biliary obstruction due to cancer, or to support the diagnosis of cirrhosis of the liver Consequently the information obtained by needle biopsy of the liver performed at the bedside was of the greatest aid

CASE II—C. K., a markedly obese housewife aged 56 years, presented a difficult diagnostic problem because of certain features suggesting parenchymal liver disease as the cause of her jaundice Six weeks prior to her hospital admission she

experienced her first attack of colicky right upper quadrant pain. This was followed, after a two-week period of anorexia, by jaundice associated with the passage of light colored stools and dark urine, and by pruritus. Prior to the onset of her presenting illness she had noted no intolerance to fatty foods and had been a hearty eater as evidenced by her weight, which was 240 pounds. Physical examination revealed the presence of jaundice several typical spider nevi were present on the anterior chest surface. Because of the marked obesity abdominal examination was unsatisfactory, the liver dullness was less than normal as determined by percussion. Ascites was not demonstrable; edema of the legs, however, was prominent.

The results of the composite liver function study are depicted graphically in Figure 64. The high serum bilirubin, negligible urobilinogen excretion, together

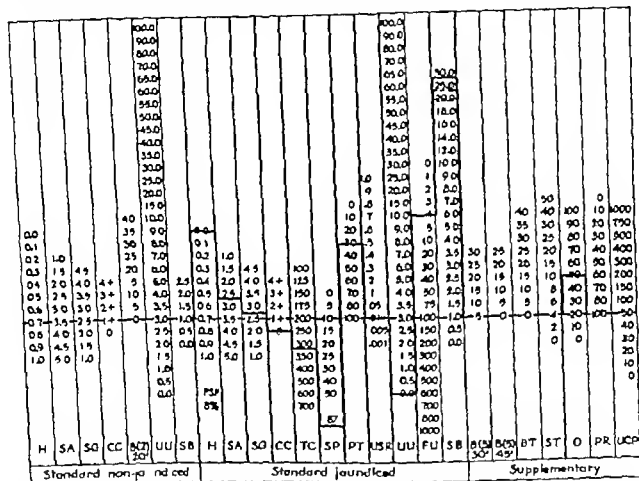


Fig 64 (Case II) —Liver function study August 25 to September 3 1944. Working diagnosis Biliary Tract Cancer or Cirrhosis. Final diagnosis Cancer of Gallbladder and Common Bile Duct. (For key to column designations, see Fig 62.)

with the elevated cholesterol and phosphatase values and the negative cephalin cholesterol, all point to a complete, extrahepatic biliary obstruction as a cause of the jaundice. The decreased plasma protein, the failure of the prothrombin value to return to normal suggest parenchymal liver damage. The validity of the low hippuric acid value is open to question since the phenolsulfonphthalein excretion during the test was only 8 per cent. Obstructive jaundice of four weeks duration does not ordinarily disturb liver function to such a degree as was evident in this instance. Allen and Jolian<sup>11</sup> cite a case of extrahepatic obstruction in which the prothrombin time failed to return to normal after adequate vitamin K therapy. That patient had common duct stones; liver biopsy revealed inflammatory changes. The appearance of spider nevi as in this case is distinctly unusual in cases of jaundice due to extrahepatic biliary obstruction.

Liver biopsy by the needle technic was not believed safe in this instance. Peritoneoscopy was considered, but abandoned in favor of exploratory operation. This decision was reached when the patient developed fever and increasing leukocytosis on the tenth hospital day. Despite the controversial evidence, the most likely diagnosis appeared to be carcinomatous biliary obstruction with cholangitis. At the time of operation, the surgeon, Dr Richard Varco, found the gall bladder to be distended and thin walled. About the gallbladder bed numerous tumor masses were found. Biopsy of one of these masses revealed squamous cell carcinoma. Biopsy of the liver was performed at operation, and the section is shown in Figure 65. This revealed a slight increase in the portal tissue mainly

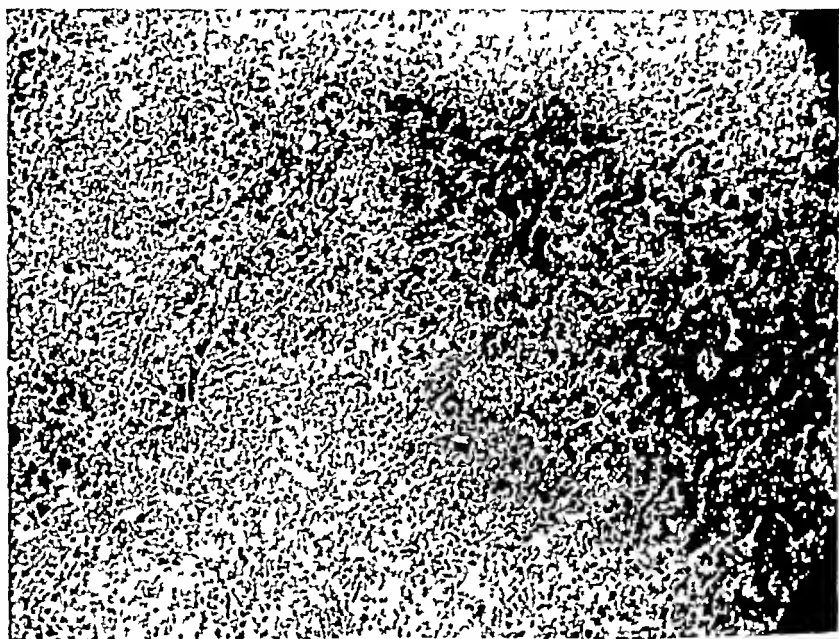


Fig 65 (Case II) —Biopsy of liver secured by the surgeon at time of operation. Extrahepatic obstructive jaundice, biliary tract carcinoma.

of the bile ducts. Numerous bile thrombi were present, no areas of necrosis were seen. Very little fat was noted.

The gallbladder was drained, a great deal of partially hemolyzed blood was found mixed with bile. Culture of this revealed aerobacter only. The patient lived but a few days postoperatively. Permission for autopsy could not be obtained. The final diagnosis was carcinoma of the gallbladder with metastases locally, and obstructive jaundice, extrahepatic in type. Of particular interest was the disturbed liver function and the presence of spider nevi simulating hepatic cirrhosis.

**CASE III**—S W., a woman aged 62, had as her chief complaint a generalized pruritus for a few years. Despite this she had not previously sought medical advice. The presence of jaundice was obvious on the first examination although the patient herself had not been aware of it. Physical examination revealed generalized brownish pigmentation of the skin, jaundice of the sclerae and a moderate degree of undernutrition. The liver and spleen were enlarged and easily palpable, there was no ascites although slight edema of the ankles was noted. Papular xanthomatous nodules were present over the Achilles' tendons and the

extensor tendons of the hands (Fig 66) The clinical impression was cirrhosis of the liver possibly of the xanthomatous biliary type



Fig 66 (Case III).—Xanthomatous nodules along the tendon sheaths. Xanthomatous biliary cirrhosis.



Fig 67 (Case III).—Needle biopsy of the liver Interpreted as portal cirrhosis.

Needle biopsy of the liver was carried out at the bedside. The histologic diagnosis from this biopsy was that of portal cirrhosis (Fig 67) A composite





and phosphatase studies, the entire picture would have been compatible with the diagnosis of ordinary cirrhosis of the liver. The enlarged liver and spleen and the jaundice without ascites suggest use of the term "Hanot's hypertrophic cirrhosis" although the age is not characteristic. While we cannot distinguish this group histologically, we recognize the clinical partition of cases of chronic jaundice, pruritus, hepatosplenomegaly and absence of ascites or of plasma albumen reduction. It is in this group that hypercholesterolemia and hyperphosphatasemia are likely to be encountered, and some few of the cases, as in the present instance, have the full-blown clinical picture of xanthomatous biliary cirrhosis.

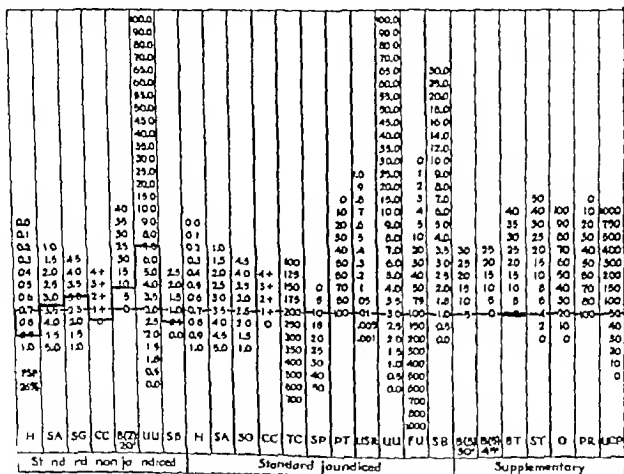


Fig 69 (Case IV) —Liver function study, September 20 to September 23, 1943.  
Working diagnosis Diabetes and Cirrhosis. Final diagnosis Hemochromatosis.  
(For key to column designations, see Fig 62.)

**CASE IV**—C. K., a farmer aged 59 years presented with the complaints of weakness, weight loss and urinary frequency. Physical examination revealed considerable pigmentation of the face, hands and arms. The liver was definitely enlarged, the spleen was not palpable. No other abnormalities were noted. Routine urinalysis revealed glycosuria and further studies confirmed the diagnosis of diabetes mellitus. The diabetes was easily controlled by dietary measures and administration of 35 units of insulin daily.

The composite liver function study is shown in Figure 69. In view of the hepatomegaly the results of the study were surprising. Only very slight deviations from normal are seen. The native urine urobilinogen was moderately elevated so that it was unnecessary to perform the stercobilin tolerance test. As a supplementary procedure, the bilirubin tolerance test was performed (Fig. 69).

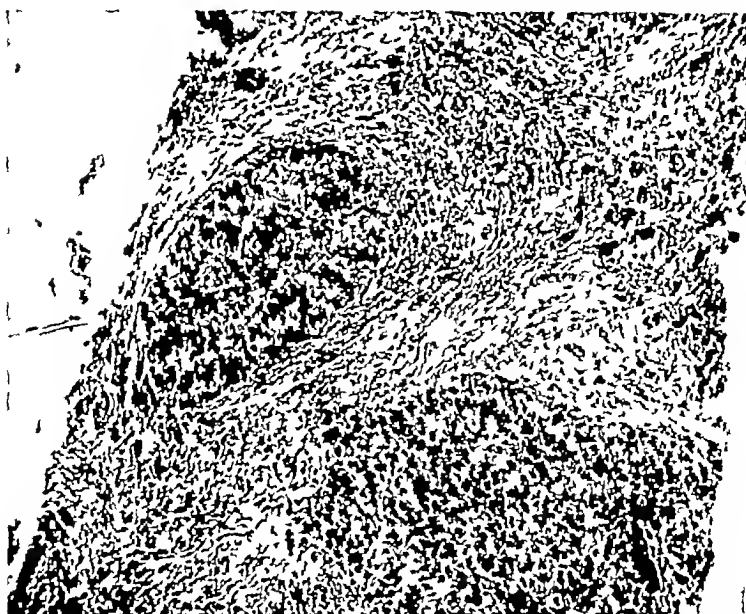


Fig 70 (Case IV) —Needle biopsy of the liver Extensive cirrhosis with some new bile ducts Note the darker masses within the hepatic cords (Hematoxylin and eosin stain)

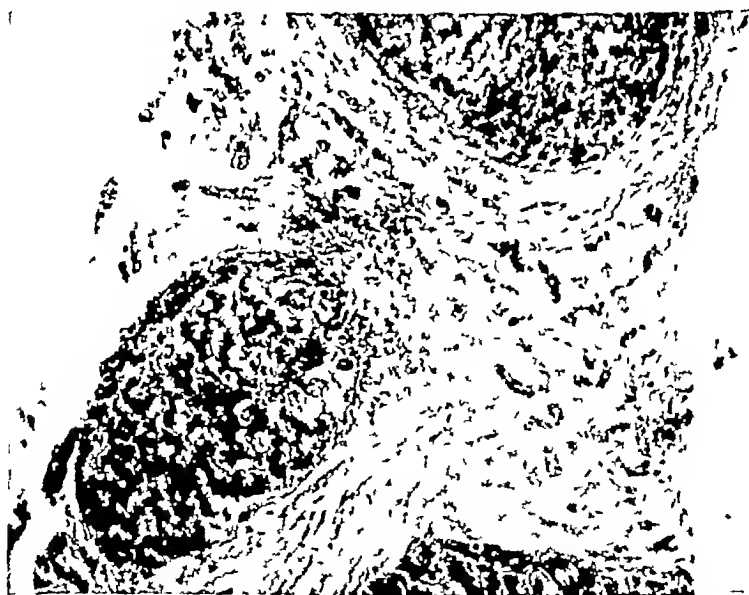


Fig 71 (Case IV) —Needle biopsy of liver as stained with Berlin blue, dark masses are a deep blue color

*BT*) The result was entirely negative This was a distinct surprise in view of the extensive histologic changes in the liver The bilirubin tolerance test is regarded by many as a delicate measure of hepatic function In our experience it has not proved to be a very useful or consistent test for clinical purposes

Because of the presence of diabetes, skin pigmentation and hepatic enlargement, the diagnosis of hemochromatosis was considered. Biopsy of the skin revealed melanin only, the sections failing to reveal any hemosiderin. The dermatologists considered that the melanosis was probably due to exposure. Needle biopsy of the liver however, clearly revealed extensive hemochromatosis and cirrhosis (Fig 70). The dark granular masses within the hepatic cords proved to be iron when stained microchemically (Fig 71).

In view of the extensive histologic changes found, the difficulty in demonstrating more in the way of functional alteration is notable. Biopsy of the liver, performed in this instance at the bedside, was the most helpful procedure in determining the correct diagnosis.

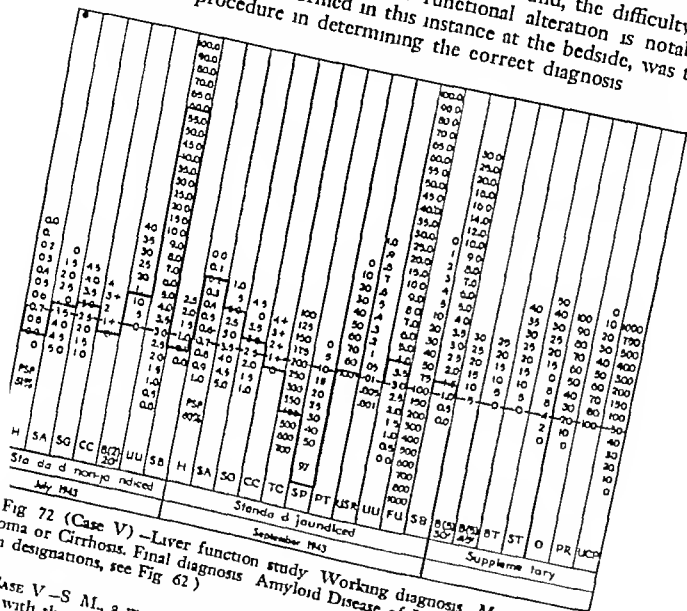


Fig 72 (Case V) -Liver function study Working diagnosis Metastatic Carcinoma or Cirrhosis. Final diagnosis Amyloid Disease of Liver (For key to column designations, see Fig 62)

CASE V-S M., a man aged 60 years, entered the University Hospital in July 1943 with the complaints of epigastric fullness, weakness, anorexia and a weight loss of 30 pounds. His first departure from good health was noted in December 1942 this consisted of postprandial discomfort. Later he noted a mass in the epigastrium which gradually increased in size.

Physical examination revealed the presence of an enlarged hard and somewhat irregular liver. No other significant abnormality was noted. Routine laboratory studies revealed no hematologic abnormalities the urine contained moderate amounts of albumin. The clinical diagnoses considered were metastatic carcinoma to the liver and hepatic cirrhosis. Roentgenologic examinations of the chest,

gastrointestinal tract and urinary tract failed to demonstrate any evidence of a primary tumor. The composite liver function study (Fig 72) performed in July, 1943, pointed to lowered hepatic function as indicated by retention of bromsulphalein and excessive urobilinogenuria. The other tests, however, yielded normal results and jaundice was absent. These results permitted no definite conclusion as to the pathology present.

Needle biopsy of the liver was performed at the patient's bedside. This revealed the presence of amyloid disease (Fig 73), a finding which was totally unexpected in view of the absence of any chronic suppuration or evidence of a neoplasm. Because of some hesitation to accept this diagnosis, the biopsy of the liver was repeated at a site somewhat removed from the former and over an area that felt nodular to palpation. The histologic examination of this second biopsy appeared to be identical with the first. In both sections, the pathologist described sheets and strands of pale-staining, faintly eosinophilic material. In some areas

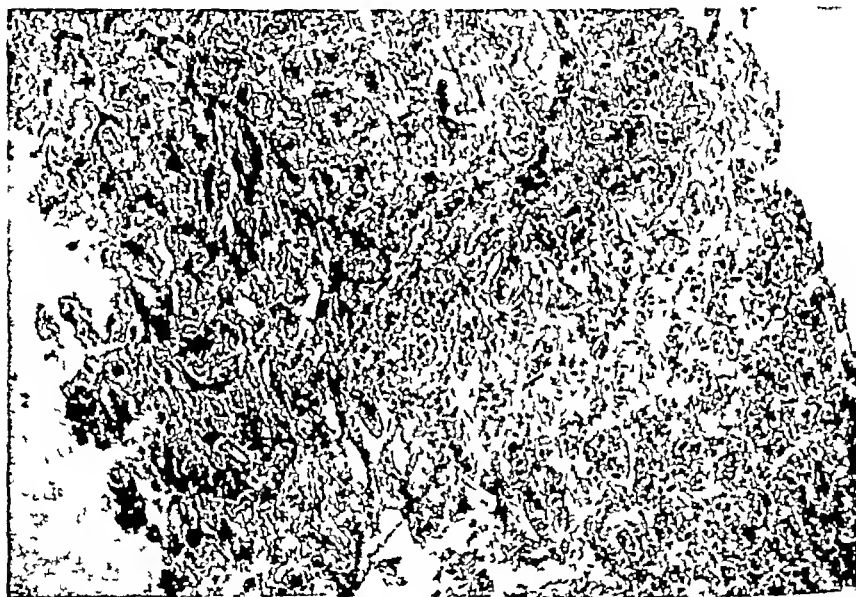


Fig 73 (Case V)—Needle biopsy of the liver, amyloid disease

this material could be seen to be definitely lining the sinusoids. The conclusion was amyloid disease of the liver.

A Congo red test performed after this information was obtained revealed 55 per cent left in the blood stream at the end of one hour.

The patient was released from the hospital. In September, 1943, he returned. Examination at this time revealed marked ascites and a greater degree of emaciation. The liver was still enlarged and the character of its surface was about the same as it had been on the previous admission. There was no visible jaundice but the serum bilirubin was 15 mg per 100 cc. The composite liver function study was repeated (Fig 72). This revealed a peculiar pattern from which no definite conclusion could be drawn. Peritoneoscopic examination was carried out during this admission. The surface of the liver as visualized appeared free of any tumor nodules. No abnormalities other than the presence of ascitic fluid were noted. Needle biopsy of the liver performed during peritoneoscopy again revealed amyloid disease. The patient remained alive for six weeks during which time he developed jaundice, later signs and symptoms suggesting adrenal insuff-



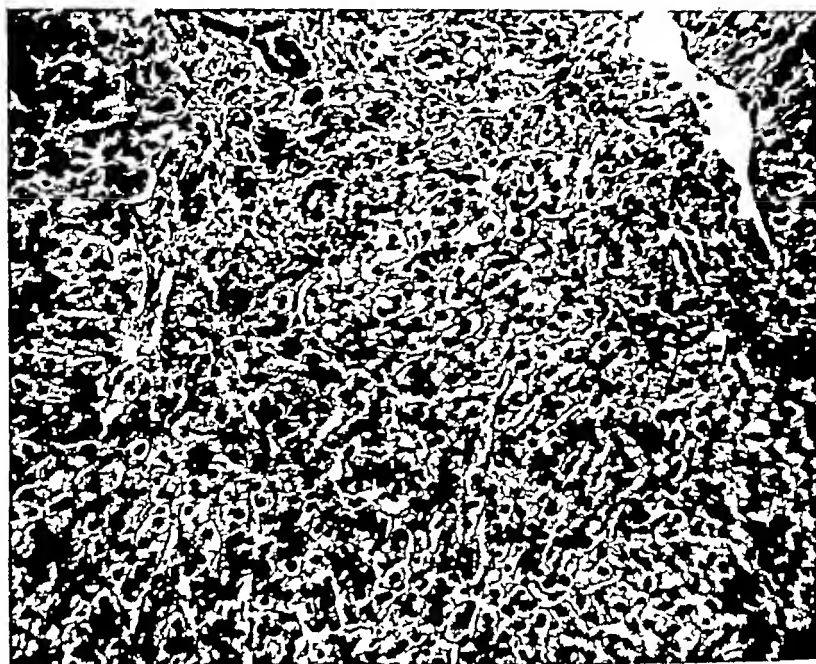


Fig 75 (Case VI) —Needle biopsy of the liver Pathological report early obstructive biliary cirrhosis

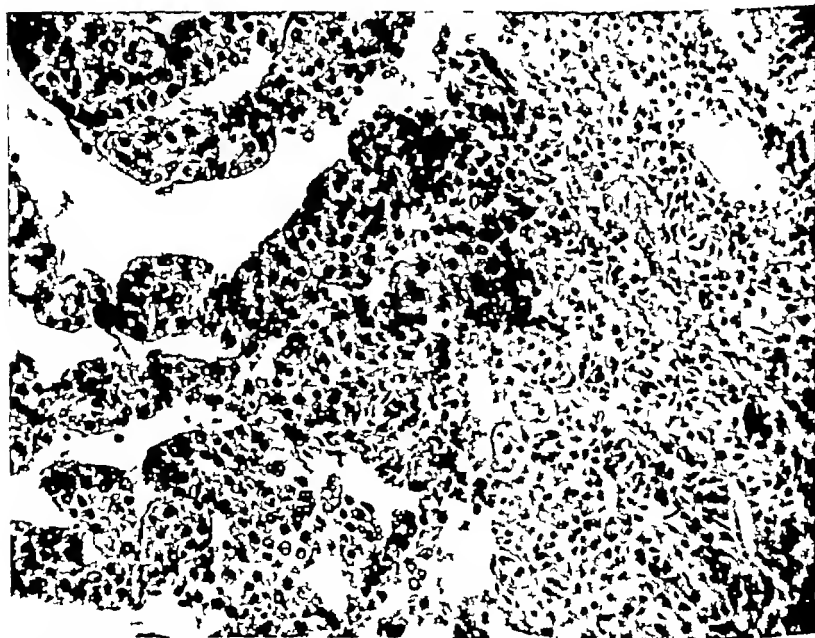


Fig 76 (Case VI) —Liver biopsy secured at time of peritoneoscopy Metastatic carcinoma adjacent to liver tissue

The composite liver function study is shown in Figure 74. This revealed a pattern indicative of complete extrahepatic biliary obstruction as seen more often with cancer. Needle biopsy of the liver was performed. A satisfactory strip of tissue was obtained which revealed evidence of nothing more than early biliary obstructive cirrhosis (Fig. 75). It was felt that the histologic changes noted could be due to long-standing biliary obstruction but the cause of this obstruction remained in doubt. The patient was therefore subjected to peritoneoscopic examination. This revealed clearly the presence of whitish nodules of various sizes on the surface of the liver. The long biopsy needle was inserted through the anterior abdominal wall and a specimen of the edge of one of the nodules was secured while the liver surface was viewed through the peritoneoscope. This biopsy revealed typical adenocarcinoma with some relatively normal hepatic cords (Fig. 76). The primary source of the carcinoma was not determined. The gallbladder as visualized during peritoneoscopy was not greatly distended. The fundus was free but the neck and cystic duct, insofar as could be seen, were involved by tumor. It was thus established that the cause of the jaundice was cancer and that this was inoperable. In this instance peritoneoscopy was the most helpful of the various methods employed, although the composite liver function study was strongly indicative of the correct diagnosis.

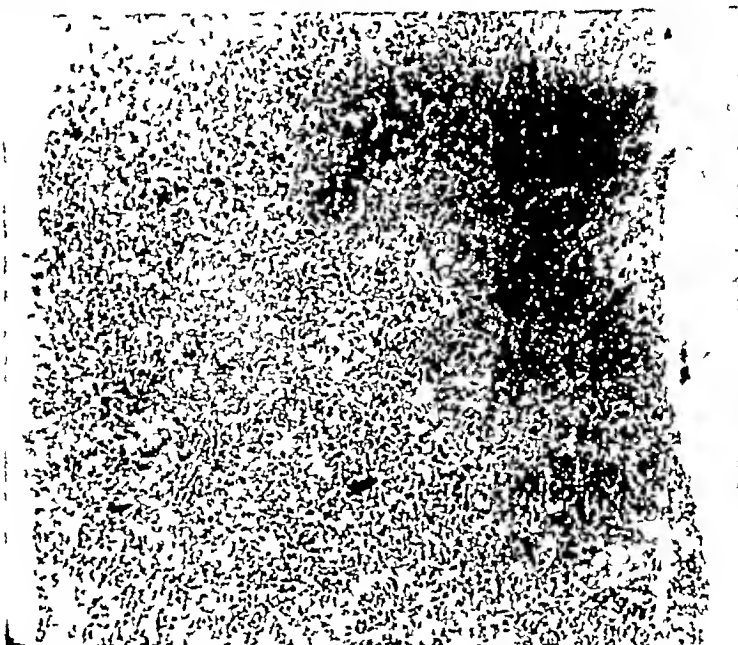
Needle biopsy of the liver when carried out as a bedside procedure is of aid in recognizing metastatic carcinoma in the liver only if the needle happens to enter a tumor nodule. Should the needle pass between the nodules, as in the case of the first biopsy in Case VI, only liver tissue is obtained and the procedure is of little value. Occasionally in the presence of suspected tumor nodules in the liver, one may feel them along the inferior margin. There is a temptation to attempt to insert the needle directly into one of them, but this is undoubtedly dangerous because of the proximity of the bowel. In such instances peritoneoscopic examination should be resorted to if the tumor nodule biopsy is deemed necessary.

**CASE VII.**—D. T., a laborer aged 53 years, was admitted to the University Hospital with the complaint of a dull constant epigastric pain. There had been no nausea or vomiting; constipation had been troublesome and he had suffered from intermittent generalized abdominal cramps associated with distention and a sensation of heaviness across the lumbar portion of his back. A detailed study in the Out Patient Clinic including laboratory and x-ray examinations had failed to yield a diagnosis. The epigastric pain had persisted for about six months.

Physical examination revealed the patient to be well developed and well nourished. There were no abnormalities noted. The abdomen was slightly distended and tympanitic. No masses were palpable. There was no adenopathy. In the differential diagnosis, atrophic cirrhosis was strongly considered and the abnormalities noted in the results of the composite liver function study tended to confirm this diagnosis (Fig. 77). The marked urobilinogenuria, the positive cephalin cholesterol flocculation and the marked bromsulfalein retention suggested parenchymal liver dysfunction. There was an absence of any qualitative or quantitative changes in the blood picture (hemoglobin 12.7 gm per cent erythrocytes 4.3 millions, leukocytes 10,300 with 73 per cent neutrophils, 25 per cent lymphocytes, 1 per cent monocytes and 1 per cent eosinophils).

During the second week of hospitalization the patient developed ascites. This made the diagnosis of cirrhosis seem all the more likely. At no time was enlargement of the liver or spleen noted. Peritoneoscopy was performed at this



[illegible]

time ascitic fluid was removed. The fluid was sterile and of low specific gravity (1.006). The liver appeared pale and finely granular. It did not have the usual appearance of cirrhosis, yet there was nothing to suggest metastatic carcinoma. Needle biopsy of the liver was performed. Bleeding, as observed, was not marked in spite of the fact that the prothrombin time was elevated and could not be returned to normal by the parenteral administration of vitamin K (Fig 77 PR). The strip of tissue obtained, while of the usual size, was hardly recognizable as liver. Large portions of the section appeared to be made up of necrotic cells (Fig 78) and one or two cords of cells embedded in fibrous tissue suggested atypical tumor cells. The final conclusion was "partially necrotic malignant tumor of liver."

The patient later developed jaundice and became comatose. He expired on the twenty fourth day of hospitalization. Autopsy disclosed the presence of Hodgkins disease involving the liver and spleen.

The clinical features of this case suggested cirrhosis, the liver biopsy was not interpreted as Hodgkin's disease, but after the autopsy had confirmed this diagnosis it was recognized that the biopsy had suggestive areas

[illegible]

Fig 79 (Case VIII) - Liver function study, October 17 to November 10, 1942. Working diagnosis: Biliary Tract Cancer or Cirrhosis. Final diagnosis: Cancer of Gallbladder and Common Bile Duct. (For key to column designations see Fig 62.)

CASE VIII.—H. C., a housewife aged 41 years, was admitted to the University Hospital because of the presence of jaundice, ascites and right hydrothorax. The jaundice had appeared four months previously. It was painless in onset. One week prior to the onset of the jaundice the patient had undergone a minor pelvic op-

eration (uterine dilation and curettage) at her local hospital Chloroform had been used as the anesthetic agent. Jaundice had been present about two months before the development of ascites. Shortly before admission to this hospital, the patient had received vitamin K therapy from her physician. Review of her past history revealed good health on the part of the patient, there was no evidence of chronic alcoholism and the only exposure to a toxic agent was the above mentioned chloroform.

Physical examination revealed a deeply jaundiced woman of the stated age, she appeared in no acute distress. The presence of hepatomegaly, ascites and right hydrothorax constituted the chief physical findings. Routine laboratory studies revealed the presence of a mild anemia, macrocytic normochromic in type. Composite liver function studies (Fig 79) revealed a pattern suggesting

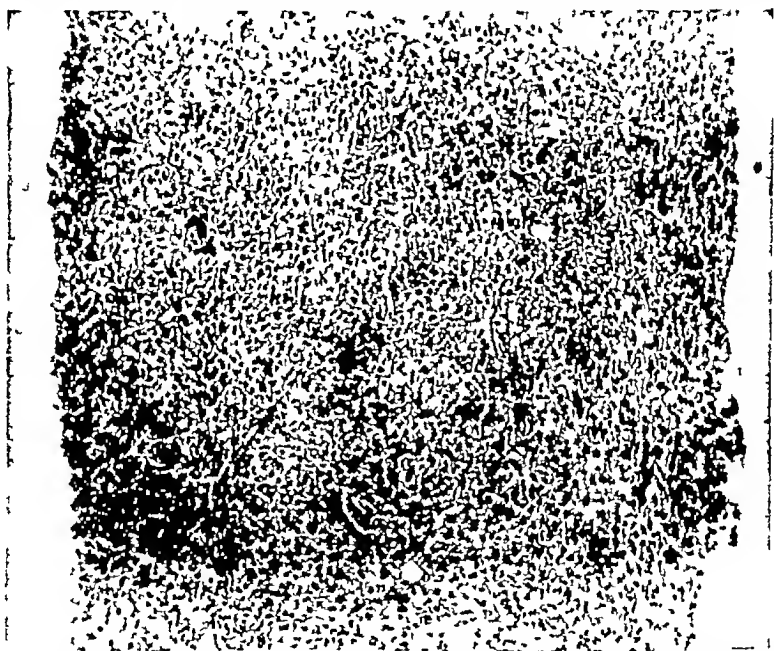


Fig 80 (Case VIII) —Needle biopsy of liver, pattern that of obstructive jaundice extrahepatic in type

complete biliary tract obstruction without much evidence of parenchymal liver damage. The hippuric acid excretion was reduced and the galactose and sterco-bilin tolerance tests revealed some abnormality. There is no doubt, however, that extrahepatic obstructive jaundice at times exhibits this much evidence of parenchymal disturbance. Needle biopsy of the liver was performed. This revealed many bile thrombi, no increase in portal connective tissue and no fatty changes (Fig 80). The pathologist, Dr J S McCartney, concluded that the appearance was that of extrahepatic biliary obstruction.

The pleural and ascitic fluids were repeatedly aspirated and searched for tumor cells. None were ever found. The clinical impression was that the patient was suffering from cancer of the biliary tract and that, in view of the ascites and pleural effusion, metastases had already occurred. The chloroform exposure was judged to be merely a coincidental matter as regards the cause of the jaundice. This proved to be correct. The patient expired three months later. Autopsy disclosed an extensive scirrhous carcinoma of the common bile duct with local and distant metastases.

## SUMMARY AND CONCLUSIONS

1 A series of cases of liver disease has been presented involving either cirrhosis or conditions in which the diagnosis of cirrhosis had to be considered. These cases illustrate many of the difficulties commonly encountered in the differential diagnosis of this group of diseases.

2 A composite liver function study has been found to be helpful. The results are recorded on a standard form permitting ready comparison of the disturbance of individual functions, together with the degree of jaundice and the degree of biliary obstruction.

3 Certain forms of cirrhosis or other liver disease, as well as extra-hepatic biliary obstruction exhibit fairly characteristic "profiles" on the composite liver function chart. It is recognized, however, that much experience must be gained before strict differentiation will be feasible on the basis of such studies, and it is certain that they will never do more than supplement the history and physical examination in any given case.

4 Liver biopsies have been carried out in seventy cases of liver disease, fifty of which were done at the bedside and twenty in the operating room under pentoneoscopic control. The Vim-Silverman needle was used in all instances. Attempts to secure a biopsy were unsuccessful in fifteen additional cases, most of which were in the earlier period of the study. A serious but nonfatal hemorrhage occurred in one instance.

5 It is believed that the conjunction of the composite liver function study with liver biopsy has permitted much additional insight into the pathologic physiology of jaundice and liver disease. From these studies it has become increasingly apparent that cirrhosis of similar anatomic extent may exhibit strikingly different degrees and types of liver functional impairment. The diagnosis of obscure or uncommon liver disorders, as for example, primary amyloidosis, has been established by biopsy in cases in which the composite liver function study, above, although abnormal, was not diagnostic.

## BIBLIOGRAPHY

- 1 Watson, C. J. *Am. J. Clin. Path.*, 14:129 (Mar.) 1944
- 2 Watson, C. J. *Wisconsin M. J.*, 43:1033 (Oct.) 1944
- 3 Ducci H. and Watson, C. J., *J. Lab. & Clin. Med.*, in press
- 4 Malloy H. T. and Evelyn K. A. *J. Biol. Chem.*, 119:481 1937
- 5 Quick, A. J. *Am. J. Digest. Dis. & Nutrition*, 6:716 (Dec.) 1939
- 6 Machella, T. E., Helm, J. D. and Chornock, F. W. *J. Clin. Investigation*, 31:763 (Nov.) 1942.
- 7 Watson, C. J. *Am. J. Clin. Path.*, 6:458, 1936
- 8 Hanger F. M., *J. Clin. Investigation*, 28:261 1939
- 9 King E. J. and Armstrong A. R. *Canad. M. A. J.*, 31:376 (Oct.) 1934
- 10 Quick, A. J. *J.A.M.A.*, 110:1658 (May 14) 1938.
- 11 Allen, J. G. and Julian, O. C. *Arch. Surg.*, 40:912 (May) 1940
- 12 Lord, J. W. and Andrus, W. W. *Arch. Int. Med.*, 68:199 (Aug.) 1941
- 13 Olwin J. H. *Arch. Surg.*, 43:633 (Oct.) 1941

- 14 Kark, R and Souter, A W *Lancet*, 2 693 (Dec 6) 1941
- 15 Lucatello, L Sulla Puntura del Fegato a Scopo Diagnostico *Lavori del Congressi di Medicina Interna, Roma, 1895*, p 327
16. Schupfer, F *Semaine Med*, 27 229, 1907
- 17 Bingel, A *Verhandl d Deutsch Gesellsch f inn Med*, 35 210, 1923
- 18 Olivet, J *Med Klin*, 22 1440, 1926
- 19 Frola, E Il Puntato Epatico Nella Diagnosi Delle Malattie del Fegato, Roma, 1935
- 20 Iverson, P and Roholm, K *Acta Med Scandinav*, 102.1, 1939
- 21 Dible, J H, McMichael, J and Sherlock, S P V *Lancet*, 2 402 (Oct 2) 1943
- 22 Baron, E *Arch Int Med*, 63 276 (Feb ) 1939
- 23 Chiray, M, Fiessinger, M and Roux, M *La Presse Med*, 49 785 (July 22) 1941
- 24 Tripoli, C J and Fader, D E *Am J Clin Path*, 11 516 (June) 1941
- 25 Silverman, I *Am J Surg*, 40 671 (June) 1938
- 26 Ruddock, J C *South Surgeon*, 8 113 (April) 1939
- 27 Benedict, E B *New England J Med*, 230 125 (Feb 3) 1944
- 28 Watson, C J *Arch Int Med*, 59 206 (Feb ) 1937 and *J A M A*, 114 2477 (June 22) 1940
- 29 Watson, C J *Proc Soc Exper Biol & Med*, 34 377, 1936
- 30 Thannhauser, S J and Magendantz, H *Ann Int Med*, 11 1662 (March) 1938

# HYPERPARATHYROIDISM

EDMUND B FLINK, MD •

HYPERPARATHYROIDISM is a disease of the parathyroid glands with its chief manifestations in the musculoskeletal and genitourinary systems. Von Recklinghausen<sup>1</sup> first described the skeletal manifestations of the disease in 1891 and differentiated osteitis fibrosa cystica from osteomalacia and osteoclastic metastases to bone.

Askanazy<sup>2</sup> was the first to comment on the presence of a parathyroid tumor in a case of osteitis fibrosa cystica. Erdheim<sup>3</sup> pointed out that the parathyroids undergo hyperplasia in osteomalacia and other bone diseases. He postulated that the abnormal amounts of calcium and phosphorus liberated from the decalcified skeleton caused hyperplasia of the parathyroids and thought therefore that in osteitis fibrosa cystica the parathyroid enlargement was a secondary phenomenon. Successful surgical removal of a parathyroid adenoma by Mandl<sup>4</sup> in 1925 with subsequent recovery of the patient disproved the belief that the parathyroid pathology was secondary to the bone disease. During the past nineteen years a great number of cases have been reported. As an illustration of the prevalence of the disease, the group of investigators at the Massachusetts General Hospital alone have treated over seventy such patients.<sup>5</sup>

## REPORT OF CASES

In order to illustrate certain diagnostic criteria and results of treatment six cases seen during the past four years at the University of Minnesota Hospitals will be reported. Particular note should be given to the skeletal and genitourinary symptoms in these cases.

CASE I.—F W., a 45 year old woman, was admitted to the hospital in June 1940. Her illness had begun insidiously six years earlier manifesting itself as muscular weakness. She had had bilateral chronic otitis media since childhood. In 1935 she had an episode of urinary frequency and nocturia but no polyuria at any time. In January 1940 an epulis was removed from the right maxilla. In March 1940 pain and a vague mass appeared in the right thigh. In April 1940 she fractured the shaft of the femur on arising from a chair. A hip spica cast was applied at another hospital. Menopause began in April 1940. The blood pressure was 104/70. There was bilateral chronic otitis media with drumhead perforations and serous drainage from each ear. Hearing was impaired moderately. A hip spica enveloped the lower body and right lower extremity. The rest of the general examination was negative.

From the Department of Medicine, University of Minnesota Hospitals, Minneapolis, Minnesota.  
Assistant Professor of Medicine, University of Minnesota.

Urinalysis and blood chemistries are recorded in Tables 1 and 2 for this and subsequent cases. The hemoglobin level was 11.4 gm per 100 cc., erythrocytes numbered 4,590,000, there were normal leukocyte and differential counts.

X-rays showed pathologic fracture of the right femur at the site of a cyst, generalized decalcification of the skeleton, coarsening of the trabeculation especially in the bones of the hands, feet and left tibia, thinning of the cortex of all bones and absence of the usual diploic marking of the skull. All these indicated a typical example of osteitis fibrosa cystica generalisata. In addition there was chronic mastoiditis.

On July 1, 1940, Dr. John R. Paine removed an adenoma of the parathyroid located in the lower pole of the right lobe of the thyroid. The adenoma weighed 3 gm and was composed of chief cells predominantly. The postoperative course was complicated by mild tetany which was controlled satisfactorily by dihydroxyacetone and calcium lactate orally. The femur fracture gradually healed. The patient's skeleton has not become completely normal after two years of follow-up, but the biochemical findings returned to normal. A mastoidectomy was carried out in 1941.

CASE II—R. S., a 38 year old woman, was admitted to the hospital in December 1941. She had noticed weakness, marked fatigability and tenderness of her knees for two years or more together with polydipsia and polyuria for seven or eight years. She had been moderately constipated for three or four years. Her principal presenting complaint was a mass in the region of the lower right molars noted first in September 1940. This mass when biopsied proved to be a giant cell tumor. X-rays of the skeleton were obtained elsewhere and she was sent to the hospital with the tentative diagnosis of hyperparathyroidism.

On examination the patient was well developed and her pulse and temperature were normal. Her blood pressure was 164/90. There was a small hard mass near the middle of the right mandible. A small mass palpated in the right side of the neck moved on swallowing. There were no areas of skeletal tenderness. The liver margin was palpable at the costal margin. The tendon reflexes were hyperactive.

The hemoglobin level was 13.5 gm per 100 cc., leukocytes and differential counts were normal. The Wassermann reaction was negative. Electrocardiograms before operation showed a first degree heart block (P-R interval 0.22 and 0.23 seconds) and an inverted P<sub>3</sub>. Seventeen days after operation the P-R interval had returned to normal (0.16 seconds), P<sub>3</sub> was upright, and the amplitude of the QRS complexes and the T waves in all leads was greater than on the initial tracing. X-rays films of the pelvis, skull, mandible, hands, long bones, vertebral column and chest revealed multiple cysts in these bones, striking nodular decalcification of the skull and generalized decalcification of the whole skeleton. There were multiple areas of calcification in the kidney parenchyma and stones in the pelvis of the right kidney.

Dr. John R. Paine carried out a subtotal resection of a large parathyroid adenoma on December 17, 1941. Ten grams were removed from the adenoma of the right superior parathyroid gland. The patient did not develop tetany post-operatively. She was readmitted to the hospital in June 1942 for removal of the remainder of the adenoma which weighed 1 gm. The adenoma was composed of chief cells predominantly. At the second admission she had renal colic and hematuria. In April 1942 there was a remarkable improvement in the appearance of the skull and in July 1942 the appearance of the whole skeleton had returned nearly to normal. The patient's weight has increased, she is able to do all of her own work, she no longer is troubled with constipation, her polydipsia is alleviated and her strength is normal. Her blood pressure was 200/110 in January 1944 and at the last visit to the clinic in August it was 146/92.

CASE III—A S., a 57 year old woman, had noted a mass in the left side of her neck for five or six years. Eructations of food began in April 1942 and vomiting after meals with serious dehydration developed in July 1942. After a period of hospitalization elsewhere her condition improved symptomatically but she was an invalid most of the time until her admission to this hospital in December 1942. Vomiting after meals and marked anorexia continued until this time. She had lost about 30 pounds of weight in all, was unusually nervous and irritable and so weak that she could not work at all. She had been constipated for many years. For five years she had noted polyuria and polydipsia but no renal colic at any time. Only on direct questioning did she admit having had some aching pains in the extremities and back.

On examination the patient's pulse was 100 and her temperature was normal. Her blood pressure was 196/114. She was tall and very malnourished, weighing 87 pounds on admission. The retinal arterioles were attenuated and there were moderate arteriosclerotic changes. A small nodular mass was located just below the thyroid cartilage on the left side in the region of the medial portion of the left lobe of the thyroid. The heart was moderately enlarged to the left. There was some thoracic kyphosis. Slowly moving peristaltic waves were visible over the stomach and small intestine. Neurologic examination was essentially negative.

Hemoglobin was 9.0 gm. per 100 cc. erythrocytes numbered 4,400,000 there were normal leukocyte and differential counts. The blood urea nitrogen obtained during the period of dehydration and eventual oliguria from fluid restriction and polyuria rose from 22 mg. per 100 cc. to 56 mg. per 100 cc. but returned to normal in twelve days. The basal metabolic rate was plus 3 per cent.

X ray films of the skull, hands, mandible, spine and long bones showed only osteoporosis consistent with her age and sex. The excretory urogram revealed poor excretion and stippled areas of calcification throughout the cortical portions of both kidneys. Chest films revealed metastatic calcification in the bronchi. The gastrointestinal tract was negative for intrinsic lesions but there was definite hypomotility of both stomach and intestine with very slow emptying time.

During preliminary investigation fluids were restricted for various reasons on four successive days. The polyuria was so marked that the patient lost 8 pounds of weight in that period and exhibited definite dehydration phenomena. On December 29, 1942, Dr. Richard Varco removed a chief cell adenoma composed of four lobules and weighing 4 gm. Three normal-appearing parathyroid glands were identified. The postoperative course was uneventful. The patient developed a moderate amount of edema during the subsequent month but this subsided following simple salt restriction and has not recurred. In four months she had gained 20 pounds in weight, was much stronger, was able to be up all day, was able to eat without vomiting and was no longer constipated. She has no polydipsia now. She is able to work as a maid all the time and her only symptom is the occurrence of an occasional severe headache. Her blood pressure was 220/120 at the last clinic visit twenty-one months after operation.

CASE IV—I O., a 57 year old woman, noted the onset of pain in the right wrist in July 1942 and in the right leg in September 1942. Severe pain on weight bearing developed in February 1943 causing her to become an invalid partially bedridden. She had noted swellings in the right forearm and right leg about the same time, and had lost 25 pounds in a year. She had polyuria and polydipsia on occasion but no renal colic or hematuria. A biopsy of the mass on her arm performed by her own physician revealed a giant cell tumor.

On examination the pulse and temperature were normal. The blood pressure was 114/78. Fusiform swellings were palpated along the midportion of the right leg and right forearm. The masses were definitely warmer than the surrounding tissue, and weight bearing caused pain. The hemoglobin was 10.9 gm. per 100 cc.



erythrocytes numbered 3,800,000, leukocytes 4100, with neutrophils 40 per cent, lymphocytes 56 per cent, monocytes 4 per cent

X-ray examination showed multiple cysts of the long bones, pelvis, skull, mandible, ribs and hands with generalized decalcification and coarsening of trabeculi. Very large multiloculated cysts in the right ulna and right tibia and multiple stones throughout both kidneys were also present. Fluoroscopy revealed a mass in the posterior superior mediastinum behind and to the right of the esophagus.

A parathyroid adenoma weighing 3 gm was removed by Drs B G Lannin and C Dennis on May 26, 1943. Postoperative tetany did not develop though the serum calcium dropped as low as 8.5 mg per 100 cc. The patient did not return to the clinic until October and then she was having recurrent pain in the right arm and leg. X-rays revealed further decalcification and new cyst formation, and she had suffered a fracture of the right tibia by stepping on a scale. She was readmitted to the hospital. A mass in the mediastinum was again demonstrated. On November 13, 1943, Dr Dennis found a parathyroid tumor in the posterior superior mediastinum and another in the substance of the left lobe of the thyroid, weighing 18 gm and 2 gm respectively. One apparently normal sized parathyroid was identified in the right superior position.

The true pathologic nature of the tumor was not appreciated until review of the sections immediately after the second operation. The histological appearance was typical of that described by Castleman and Mallory<sup>6</sup> as primary hyperplasia of the "wasserhelle" cells. Postoperative tetany did not occur. The patient improved gradually and gained weight, but has had bone pain from time to time. A letter from her in August 1944 stated that she was feeling better than she had for a long time, but she had not returned to the clinic for determinations of serum calcium, and so on. One cannot say that she is cured at the present time, but she is improved.

**CASE V—S F** (Reported through the courtesy of Dr George Levitt of St. Paul, Minnesota.) This 40 year old woman was admitted to the University Hospital in December 1943 for the confirmation of a diagnosis of hyperparathyroidism. In the early part of 1940 she had a vaginal hysterectomy for excessive uterine bleeding (benign). Immediately thereafter she noted severe pains in her lower back and left hip and thigh. These pains were excruciating on any kind of weight-bearing but were present to some degree all the time. Muscle weakness since the onset in 1940 had prevented her from performing more than a part of her household duties and had resulted in complete exhaustion on walking two blocks. During 1943 the pains in the legs, hips, ribs and upper back were constantly present, and deformity of the terminal phalanges of both hands began and progressed without any noticeable joint involvement. Since 1940 she had had bouts of polydipsia and polyuria but no other renal symptoms.

On examination the pulse and temperature were normal. The blood pressure was 138/80. A moderate thoracic kyphosis was evident. A mass which was vaguely defined was present under the origin of the sternocleidomastoid muscle in the region of the lower pole of the left lobe of the thyroid. Tendon reflexes were equal but slightly hyperactive. There was marked deformity of the hands, most marked in some of the terminal phalanges but also present in some of the middle phalanges.

The hemoglobin was 13.6 gm per 100 cc, leukocytes numbered 4350, with neutrophils 60 per cent, lymphocytes 36 per cent, monocytes 2 per cent and eosinophils 2 per cent. The Kline exclusion test was negative.

X-ray films taken elsewhere in 1941 showed changes in the skull, ribs, hum

crus, pelvis and thoracolumbar spine with decalcification and tendency to cyst formation. Typical changes of *ostitis fibrosa cystica generalisata* with especially marked changes in the phalanges of the hands were present in 1943.

The patient was referred to Dr. Oliver Cope of the Massachusetts General Hospital who removed a chief-cell adenoma of a parathyroid gland. Mild symptoms of tetany developed immediately postoperatively but the symptoms have been completely alleviated. Eight months after operation the calcium phosphorus and phosphatase values were normal.

**CASE VI**—G. M., a 59 year old man, was admitted to the hospital on April 2, 1944. Two years before he fell and injured his left knee. The injury was treated by the application of a cast, but it was not certain whether he had a fracture. Since that time he had had pain in the lower back, in the hips and both lower extremities. The pain was deep-seated, often shooting in character and severe enough to require opiates for relief. The patient had been weak for twelve years and for three years the weakness had been progressively interfering with his work. For twenty five years he had had polydipsia of varying intensity and had had to drink as much as 2 gallons of water some days. There had been no other renal symptoms. He had lost 30 pounds during the past several years in spite of a good appetite.

Examination showed a well developed but very poorly nourished man weighing 120 pounds. His blood pressure was 113/72. A small mass was palpable below the right sternocleidomastoid muscle at the level of the lower pole of the right lobe of the thyroid. This mass moved on swallowing. He had a lumbar lordosis and a slight thoracic kyphosis. There was slight inequality of the tendon reflexes, but sensory examination was normal.

Hemoglobin was 12.1 gm per 100 cc., erythrocytes numbered 3,760,000, leucocytes and differential count were normal. The blood urea nitrogen was 45 mg per 100 cc. and the creatinine 2.3 mg per 100 cc. before surgery. Several weeks after surgery the blood urea nitrogen had decreased to 17 mg per 100 cc. An electrocardiogram revealed a P-R interval of 0.20 seconds.

On x-ray the skull showed an extremely granular appearance similar to that of patient II. Some rarefaction of the mandible was evident as well as a marked osteoporosis of the hands with thinning of the cortices of the small bones, erosion of many of the distal phalanges and fracture of some of the terminal tufts. Both tibiae and fibulae showed extensive decalcification with some granularity and thinning of the cortex. There was evidence therefore of a severe form of *ostitis fibrosa cystica generalisata*.

In May 1944 Dr. Richard Varco removed a parathyroid tumor weighing 20 gm from the region of the lower pole of the right lobe of the thyroid and the subclavicular area. The adenoma was composed of chief cells predominantly. In some areas there was a tendency to rosette formation and gland formation. Normal parathyroid glands were identified on the left side.

On the seventh postoperative day the patient had definite but mild symptoms of tetany. For several days his Chvostek and Trousseau signs had been positive and remained positive for four or five days thereafter. He received 1 gm of calcium gluconate on three occasions with satisfactory response. On the day of operation and during the whole postoperative period he received 3.75 mg of dihydrotachysterol and 6 to 24 gm of calcium lactate orally every day. In the three-month period from operation to the last clinic visit he had gained 15 pounds, was much stronger, was practically free of pain and his morale was much better. There had been a remarkable increase in the calcification of the skull and skeleton in general but not a complete return to normal.

## COMMENT

**Diagnosis**—A clue to the diagnosis depends on the symptomatology which is characteristic of the disease. The musculoskeletal and genitourinary symptoms predominate, but gastrointestinal and cardiovascular symptoms may occur and may even be the presenting complaints.

The most prominent symptom of all is *pain in the bones and joints*. The six patients had a variable amount of pain. In Case VI the patient had so much pain that he had to take codeine frequently and was disabled for two years. His pain was erroneously thought to be due to polyneuritis when he was first seen at this hospital. In all of the patients the pains were not constant but were severe at times and practically absent at other times. Pain on weight bearing is an important symptom and should suggest some form of bone disease. This symptom could be elicited from five of the six patients. Direct questioning in Case III was necessary to elicit the history of mild pain in the bones and joints.

All patients exhibited *muscular weakness* which was marked enough to interfere with work, and even caused semi-invalidism of several patients. The muscular weakness is probably related to the hypercalcemia. It is interesting that some of the patients had hyperactive tendon reflexes.

An *epulis* was removed in the first two patients some time before the true nature of the disease was recognized. Epulides are well known in a small percentage of cases of hyperparathyroidism. Thannhauser<sup>7</sup> reports the presence of epulis-like lesions in cases of bone disease associated with neurofibromatosis.

Deformities of any part of the skeleton may occur. There have been many patients with progressive decline in stature because of compression of the vertebral bodies, coxa vara, and bowing of the long bones. None of the six patients in the present series complained of change of stature, but several had moderate kyphosis. Deformities of the hands in Cases V and VI and tumefactions in some of the long bones in Case IV and in the femur in Case I were noted.

A pathologic fracture of the right femur was responsible for bringing the first patient to the care of physicians. Interestingly enough it was thought that she had metastatic carcinoma of the femur and she was transferred to this hospital for palliative x-ray therapy. *Fractures sustained by little or no trauma* certainly should suggest the possibility of hyperparathyroidism or some other decalcifying or cyst-forming process. They constitute presenting complaints of a fair percentage of patients with this disease.

**Genitourinary Symptoms**—A better understanding of the symptomatology referable to the genitourinary tract has resulted from the classification proposed for the renal pathology by Albright and associates.<sup>8</sup> There are three main groups of lesions: (1) pyelonephritis secondary to formation of calcium phosphate stones, (2) nephrocalcinosis,

differing from the previous type in that the calcium deposits are in the kidney parenchyma rather than in the pelvis, and causing inflammatory changes, sclerosis and contracted kidneys, (3) acute parathyroid poisoning with calcium deposits in the kidney and all other organs, resulting in anuria and death. The symptoms associated with formation of stones in the pelvis or ureters are the same as those from any stone. Renal insufficiency may occur from hydronephrosis and pyelonephritis. Particular attention should be given to the symptoms of polydipsia and polyuria. Five of the six patients in this series had polyuria either constantly or intermittently before operation. The urine volumes were as high as 3000 cc. per day but averaged 1500 to 2000 cc. during hospital stay before operation. The cause of the polyuria is not entirely understood, but it was present in a patient with normal renal function and was alleviated after operation in all but one patient. It must be related in some way to hypercalcemia, hypercalciuria and hyperphosphaturia. In two patients (Cases III and VI) these symptoms were the first real clue to the diagnosis. It is entirely possible that a correct diagnosis would not have been made in Case III if they had not attracted attention to the possibility of hyperparathyroidism. The polyuria was so marked that dehydration occurred when fluids were restricted. The sixth patient was in the hospital for twenty days before the symptom complex of pain in the extremities and polyuria was recognized.

*Cardiac irregularities* and conduction defects occur occasionally. In Case II the patient had a prolonged P-R interval which returned to normal after operation. Elsom, Wood and Ravdin<sup>9</sup> reported a patient with prolonged P-R conduction time which did not return to normal after removal of a parathyroid adenoma. Hypertension is related to renal insufficiency but patients IV and VI with renal insufficiency of a severity comparable to that of the two hypertensive subjects, had normal blood pressures. Snapper<sup>10</sup> followed a patient with hypertension for two years after removal of a parathyroid adenoma and found persistence of the hypertension. The absence of hypertension in some patients with severe renal insufficiency has been noted by others.<sup>7, 9, 10</sup> No striking improvement in renal function occurred in the patient reported by Elsom and his coworkers<sup>9</sup> in one year following removal of a parathyroid adenoma. This has been the experience of others.<sup>8, 10</sup> It is reasonable, however, to expect cessation of the progress of renal insufficiency by successful surgical treatment of hyperparathyroidism. In Cases III and VI a moderate improvement in renal function has been evidenced by a decrease in blood urea nitrogen to normal and an increase in phenolsulfonphthalein dye excretion. Hypertension has persisted in Cases II and III.

Many patients have *constipation* and *flatulence*, and some have marked *anorexia*, *nausea* and bouts of *vomiting*. The third patient had unusually severe gastrointestinal symptoms. She was admitted to the

hospital because of recurrent vomiting. She said "The food just doesn't go down." Pyloric obstruction was suspected clinically and a gastrointestinal study by barium meal was carried out. There was no obstruction but the stomach and bowel motility was very slow. Morelle and Beyerinck<sup>11</sup> have each reported an instance of similar severe gastrointestinal symptoms. One must consider this disease in patients with symptoms suggesting pyloric or intestinal obstruction.

*Roentgenologic Diagnosis*—The roentgenologist often suggests the diagnosis of hyperparathyroidism when it has been unsuspected clinically. Osteitis fibrosa cystica generalisata does not occur in all cases as illustrated in Case III, and especially in cases reported by Albright and his coworkers.<sup>12</sup> The bone lesions are generalized when they are demonstrable. There is widening of the bone marrow space with thinning of the cortex. The diffuse widening of the Haversian canals becomes evident as increased porosity of the bones and increase in the coarseness of the trabeculation of bone. Cysts and giant cell tumors occur frequently but these are not necessarily present. The skull often has a very characteristic appearance. Unusual skull changes were seen in Cases II and VI. X-ray demonstration of renal calcification, calcium phosphate stones in the renal pelvis and metastatic calcification in other organs is very important information. Fluoroscopy, x-rays, and plainograms of the upper mediastinum are valuable in trying to locate adenomas in the mediastinum.

*Biochemical Diagnosis*—As valuable as x-ray diagnosis is in this disease, confirmation of the diagnosis depends on the biochemical findings in any given case. The essential features of the biochemical syndrome are as follows: (1) hypercalcemia, (2) hypophosphatemia, (3) hypercalciuria, (4) hyperphosphaturia and (5) increase in the phosphatase content of the serum. Parathormone causes an increase in the serum calcium, reduces the serum phosphate, and in young animals especially will cause widespread bone disease similar to osteitis fibrosa cystica. Furthermore it has been amply demonstrated that parathormone causes a phosphate diuresis.

A complete calcium balance study was not carried out in any case of the present series, nor was phosphorus excretion studied. In Table I the chemical findings in the six cases are summarized. There are some unexplainable variations in the data, but for the most part the findings are self-evident. McLean and Hastings<sup>13</sup> have demonstrated the importance of a consideration of serum protein in conjunction with serum calcium determinations, since the nondiffusible portion of the total calcium depends entirely on the protein concentration. In other words, lowering of serum proteins will lower the total calcium approximately 0.75 mg. for each gram of protein. The importance of this factor is especially evident in the interpretations of the serum calcium in Case III, when the calcium concentration was 9.8 mg. per 100 cc., the total serum protein was only 5 gm. per 100 cc.

TABLE 1—CHEMICAL FINDINGS

Case No.	Preoperative					Postoperative				
	Serum Calcium mg./100 cc.	Serum Phosphorus mg./100 cc.	Serum Protein gm./100 cc.	Serum Phosphatase units/100 cc.	Urinary Calcium mg./day	Serum Calcium mg./100 cc.	Serum Phosphorus mg./100 cc.	Serum Phosphatase units/100 cc.	Urinary Calcium mg./day	
I	12.4	2.3		38 B U		7.1	2.3	20	5.7	
	12.8	2.0				9.7	4.5		65.0	
II	12.5	1.8			52.5	10.1 (25)†	3.7 (25)	13.5 (25)	17.0 (9)	
	16.0	2.6	6.2	77	387	9.4	3.6	54	0	
III	15.2	2.3		89	311			8	32	
	15.7	4.0	5.5	8	259	10.2 (14)	2.4 (14)	7.7 (14)		
IV	11.8	3.4		10	491	10.7	3.3		225	
	9.6	1.9			431	11.0	2.9		193	
1st admission	9.8	3.4	5.0		269	9.6	3.4		56	
	11.0	3.4			508	8.5	3.4		63	
2nd admission	12.8	2.9	6.6	39	274	11.1 (22)	2.9 (22)	8.9 (22)	75	
	13.8	2.1		50	269	8.4	2.7		58	
V	12.1	2.0			321	12.7	2.3		198	
	11.6				392				164	
VI	14.1	2.7	7.0	67	237	10.7	2.3	53	57	
	11.7	1.6			184	9.1	2.8	59	190	
VII	15.7	2.7			263	9.6	2.4	45 (5)	236 (5)	
						8.1 (2)	1.5 (2)			
VIII	12.5	1.7	7.0	104	248	10.1 (8)	4.7 (8)	14 (8)		
	13.0	1.9			180					
IX					180					
					228					
X	17.6	4.2	6.7	50	256	10.8	1.6		+	
	16.5	2.2			208	9.7			0	
XI	14.5				161	7.5			0	
						7.0			0	
XII						9.8 (1)	2.8 (1)	40 (3)	trace	
						8.5 (3)	3.6 (3)			

Serum alkaline phosphatase units are expressed as King-Armstrong units/100 cc.

† Preoperative values on emergency admission.

Serum alkaline phosphatase units are expressed as King-Armstrong units/100 cc. serum in all instances except the first marked B.U. = Bodansky Units.

† Preoperative values on successive days were obtained when the patient was eating a general diet often with extra calcium.

‡ Numbers in parentheses indicate number of months after operation.

§ Postoperative values were obtained when the patient was eating a low calcium neutral salt diet and the postoperative values were obtained when the patient was eating a general diet often with extra calcium.

In a review of 114 cases of hyperparathyroidism in which the serum calcium concentration was recorded, Gutman and coworkers<sup>14</sup> found that 109 had over 11 mg and 91 had over 12 mg per 100 cc. In 79 cases in which the serum inorganic phosphorus was recorded 35 cases had values less than 2.5 mg per 100 cc. Albright and associates<sup>12</sup> reported a number of instances of proven hyperparathyroidism in which the average calcium concentration of the serum was below 12 mg per 100 cc and in which the serum phosphatase activity was entirely normal. These patients had symptoms referable to genitourinary tract calculi and were classed as "cases with a minimal degree of hyperparathyroidism." The average preoperative serum calcium values reported in this series of 35 cases ranged from 10.6 to 17.3 mg per 100 cc. It is important to recognize that when serious renal insufficiency and uremia supervene, the phosphorus may be normal or even high and consequently the serum calcium may be normal or even low. Many authors have emphasized the importance of repeated calcium determinations in a case of suspected hyperparathyroidism and one can understand the importance of this when one reviews the data in Case III and in other reported cases. For instance Wilder and associates reported a case with extreme skeletal decalcification having serum calcium values of 11.5, 11.0, 10.6 and 11.0 mg per 100 cc.

*Calcium excretion in the urine* is an important confirmatory test, especially when the results of the chemical analysis of the serum are unconvincing. This was of crucial importance in Case III. The qualitative Sulkowitch test<sup>16</sup> indicates roughly the presence of abnormal amounts of calcium, but because of variations in specific gravity and volume of the urine from time to time, quantitative information is to be preferred. The urine calcium determinations in the present study were carried out by an adaptation of the Sulkowitch test for use with the Evelyn photoelectric colorimeter. The turbidity formed by the calcium oxalate precipitate depends on the quantity of calcium oxalate and can be measured with the colorimeter quite accurately. A low calcium neutral-ash diet was given preoperatively but high calcium intakes were given postoperatively. A normal person excretes 100 mg calcium or less in the urine daily when taking the above diet. All of the patients in the present series had increased excretion of calcium. It may be noted that patient VI had lower calcium excretion than the others but his renal function was seriously impaired. Snapper<sup>10</sup> reported a case in which the urine calcium excretion was entirely normal, but his patient had renal insufficiency as evidenced by slightly elevated blood urea and nonprotein nitrogen. Downs and Scott<sup>17</sup> reported a case with an excretion of but 24 mg of calcium per day during the phase of uremia. A negative calcium balance and a high excretion of calcium in the urine also occur in hyperthyroidism, in multiple myeloma, and in Paget's disease of bone. These conditions have to be di-

TABLE 2—RENAL STATUS

Case No.	Urinalysis			Renal Function		
	Specific Gravity	Albumin	Sediment	Phenothalpoephthalein		Blood Urea Nitrogen
				15 Minutes	2 Hours	
I	1004-1016	0-trace	0 to many W.B.C.		60% 70% (2)†	10
II	1005-1015	0-1+	0 to many R.B.C.	15% 10%	48% 30% (6)	22 24
III	1015-1008	0-trace	0	4% 5%	14% 15%	56 72 19 (18) 16 (22)
IV	I. 1004-1011 II. 1008-1011	0-1+ trace	0 to many R.B.C. 0 to many R.B.C.	5%	45% 33%	
V	1010-1018	0	0	50% (30 min)	68%	
VI	1008-1013	0-trace	0 to occasional R.B.C.	2% 2%	10% 24% (14)	45 17 (4) 21 (1)
						Ca 27% Ca 26%

The patient was dehydrated and had an oliguria at time of these determinations.

† Numbers in parentheses indicates number of months after operation.



ferentiated from hyperparathyroidism by serum calcium and phosphorus determinations and evidence obtained by x-ray examinations.

The *alkaline phosphatase activity of the serum* is considered to indicate the activity of the mechanism of bone repair even though in hyperparathyroidism osteoclasia is the process most evident histologically and by x-ray. There are many other conditions of the bone in which the phosphatase activity is increased, particularly in Paget's disease of bone, in rickets, in osteomalacia, in certain cases with carcinomatosis of the skeleton and in extensive fractures. In multiple myeloma and Ewing's tumor the phosphatase activity is usually within normal limits. Cope and Churchill<sup>18, 19</sup> and Albright and coworkers<sup>12</sup> have shown that the higher the phosphatase activity preoperatively the greater is the possibility of tetany after complete removal of an adenoma or subtotal removal of hyperplastic tissue. No correlation exists, however, between the height of the serum calcium and the probability of tetany. Thus if the preoperative phosphatase determination is high, postoperative tetany should be looked for and treated as soon as premonitory symptoms develop.

*Pathology*—The total weight of the normal parathyroid glands is 0.11 to 0.13 gm. There are usually four glands but as few as two and as many as six have been found in a given subject. The glands are composed of four kinds of cells: the chief or principal cell, the "wasserhelle" cell, the pale oxyphil cell, and the dark oxyphil cell.

The pathology of the parathyroid tumors has been worked out by Castleman and Mallory.<sup>6</sup> "It was found possible to divide the cases sharply into two groups: one of them characterized by diffuse uniform changes throughout all the glandular tissue—an obvious hyperplastic process—the second by a proliferative area limited to one gland, frequently even to a portion of it, or rarely involving parts of two glands—neoplasia." Seven of seventy cases reported by Cope<sup>5</sup> were examples of diffuse hyperplasia of the water-clear cells. Patient IV reported above had primary hyperplasia of the wasserhelle cell type. It is noteworthy that this was not recognized at the first operation making a second operation necessary. The pathologic condition now recognized as primary hyperplasia, usually of the wasserhelle cells, is extremely important in that failure to recognize it will account for failure to correct the disease. Two adenomas of chief cell type may occur in the same patient and may account for residual disease after removal of a single adenoma.<sup>18</sup>

Adenomas usually weigh from 0.5 to 20 gm. but one weighing 101 grams<sup>20</sup> has been reported. They are composed predominantly of chief cells but in rare instances oxyphil cells predominate. Rosette formation and pseudoglandular appearance, as in Case VI, occurs in some cases. Gentile and associates<sup>21</sup> reported a case with typical symptoms of hyperparathyroidism caused by a malignant parathyroid tumor which metastasized locally, resulting in recurrence of symptoms cor

rected by a second operation. Many malignant parathyroid tumors without hyperparathyroidism have been reported.

Secondary hyperplasia of the parathyroid glands occurs in renal insufficiency, in rickets, Paget's disease, osteomalacia and occasional instances of metastatic cancer of the bones. This hyperplasia is characterized by a predominance of chief cells in contradistinction of the predominance of wasserhelle cells in primary hyperplasia.

**Differential Diagnosis.**—Of course many bone diseases have to be considered in the differential diagnosis of hyperparathyroidism with skeletal involvement. *Paget's disease* is never generalized. The x-ray appearance is diagnostic, there is no disturbance of serum calcium and inorganic phosphorus concentrations, but there usually is considerable increase in serum phosphatase. *Multiple myeloma* may be generalized but the x-ray appearance is usually diagnostic. The phosphatase is usually normal and serum inorganic phosphorus is normal. Hypercalcemia and hypercalciuria may occur rarely. In addition there is often hyperglobulinemia so that the erythrocyte sedimentation rate is very rapid and excessive rouleau formation is noted (so-called "greasy blood smear"). Bence-Jones protein is present in the urine of a majority of patients. Generalized *cancer metastases* to bone rarely cause generalized decalcification. The serum inorganic phosphorus is almost always normal even though the calcium may be increased. Histological evidence of metastases may be the only diagnostic feature, but usually the x-ray appearance and clinical features suffice to differentiate this bone disease from the others. *Hyperthyroidism* offers a special problem in that nervousness and irritability are common to both diseases. The skeleton may be very extensively decalcified. The serum inorganic phosphorus is normal, the phosphatase is normal or very slightly elevated and of course calcium excretion in the urine usually is considerably increased. Of course the usual evidence of hyperthyroidism is very important. *Lipoid granulomatosis*, i.e. Hand-Schüller-Christian disease can be differentiated readily by x-ray examination. *Osteomalacia* and *renal osteodystrophy* have characteristic biochemical findings. A condition variously named *osteitis fibrosa cystica disseminata*, fibrous dysplasia of bone, and Albright's disease has caused much confusion and has led to erroneous diagnoses of hyperparathyroidism. This disease is characterized by brown spots (café au lait spots) on the body, soft tissue tumors (neurofibromata) occasionally precocious puberty in females and involvement of any part of the skeleton often just on one side of the body but never generalized. It is a variant of neurofibromatosis. An excellent review of this disease has recently been provided by Thannhauser.<sup>7</sup>

**Treatment.**—*Surgery.*—The principles and technic of surgery of the parathyroids have been thoroughly discussed by Cope and Churchill<sup>10</sup> and the reader is referred to their papers. The preoperative diagnosis must be firmly established for in this disease the diagnosis

cannot be excluded by a single exploratory operation. The surgeon should be thoroughly convinced of the accuracy of the diagnosis. The most meticulous and thorough dissection is necessary in order to find small adenomas and, more important still, in order to identify and not interfere with normal parathyroid tissue. Cope has discussed the practical relations of embryology of the glands to possible aberrant positions. Sixteen out of sixty patients had tumors in the anterior or posterior mediastinum. Four out of fifty-four had two adenomas. When one fails to find a tumor or hyperplasia in the neck region, the posterior superior mediastinum can be explored from the neck, but when this fails also, a second operation with reflection of the upper part of the sternum for exploration of the anterior mediastinum must be carried out. Subtotal resection of a solitary adenoma is recommended if no normal parathyroid tissue is recognized or if there is a very high phosphatase and renal insufficiency. It is extremely important to have rapidly frozen sections and histologic examination of any tissue removed at operation to identify it as parathyroid tissue and also to detect primary hyperplasia.

Oliguria and retention of nonprotein nitrogenous products may be serious complications in the immediate postoperative period. During the operation the administration of 5 per cent glucose solution in distilled water intravenously by constant drip and after the operation the administration of 3000 cc or more of fluids per day, parenterally as necessary, are important measures in preventing oliguria. Calcium salts for intravenous use should be available for prompt administration to alleviate tetany if it is severe.

*Prevention of Tetany*—The surgical principles and technic outlined by Cope and Churchill were followed in most of the present cases but in Cases I and VI total resections were carried out even though tetany was to be expected. Normal parathyroids were identified in each instance. Particularly in Case VI expectation of the development of tetany was great and, to be sure, he did develop mild tetany on the seventh day, but he was carefully watched and vigorously treated from the onset. In Case I the mild symptoms of tetany were easily controlled by the administration of 1.25 mg of dihydrotachysterol and 6 gm of calcium lactate orally each day for one month. Patient VI received dihydrotachysterol continuously from the day immediately before surgery in a dose of 3.75 mg per day for the first month. Then the dose was reduced to 1.25 mg per day. Calcium lactate in doses ranging from 6 to 24 gm per day was also given orally. It was necessary to administer calcium gluconate intravenously on three occasions for the control of minor tetanic symptoms. Because of the calcemic effect vitamin D<sub>2</sub> could be used in large doses (from 100,000 to 400,000 units a day) to as good advantage for it has been demonstrated that such doses are just as effective as dihydrotachysterol.<sup>22</sup> It is suggested that prophylactic administration of either substance together with cal-

cium salts, from the day of or the day following surgery until the danger of tetany is passed, may prove to be of definite benefit in preventing or minimizing tetany postoperatively. The use of the Sulkowitch test at frequent intervals is of much assistance in anticipating the onset of tetany and in judging a safe dose of the drug, complete absence of a precipitate indicates serum calcium of 8 mg per 100 cc. or lower and a heavy precipitate indicates high calcium levels. If a tumor is not found at operation no harm can be done by a single or even several doses of dihydrotachysterol and the drug can be discontinued.

*Follow-up Program*—A follow-up of every patient for a number of years is necessary to be sure that recovery has occurred or that recurrence does not go on untreated. It is difficult to define an adequate follow-up program, but certainly the main features of the biochemical syndrome should be checked every three months for a year and then every six months for a while. X-rays of the skeleton should be taken according to the symptoms and other progress. The first patient has been lost sight of and the fourth patient has failed to return at the appointed interval, so that our own follow-up has not been ideal.

Improvement of the skeleton can be attained without surgery by the administration of large amounts of calcium, but such treatment has resulted in further renal damage and certainly should not be pursued. X-ray treatment of the region of the neck has been without avail in carefully studied cases and should be abandoned as a form of treatment, for it can only delay adequate surgical treatment and delay may be costly, particularly as far as the kidneys are concerned.

### SUMMARY

Six cases of hyperparathyroidism are described. Many of the problems, some of the pitfalls, most of the symptoms, and the major pathologic groups of the disease have been encountered. Stress has been placed on the symptomatology referable to the skeletal and the genitourinary systems as the most important clue to diagnosis. Polyuria as a single symptom was the initial clue in two patients who had been diagnostic problems at this and other hospitals and clinics. The biochemical findings in each case were diagnostic. Osteitis fibrosa cystica generalisata was present in five cases. One patient has osteoporosis comparable in severity to that which could be expected normally at her age, furthermore, the phosphatase activity of her serum was normal. A method of prophylaxis or amelioration of postoperative tetany has been suggested and tried in several patients, and should be given further trial. The use of the Sulkowitch test at frequent intervals to anticipate hypocalcemia and tetany in the postoperative period has been found to be very valuable.

## BIBLIOGRAPHY

- 1 Von Recklinghausen, F Festschrift der Assistenten fur Virchow Berlin, 1891 Cited by Snapper,<sup>10</sup> p 5
- 2 Askanazy, M Arbeiten auf dem Gebiete der pathologischen Anatomie und Bakteriologie, Vol 4, page 398, 1904 Cited by Snapper,<sup>10</sup> p 10
- 3 Erdheim, J Rachitis and Epithelikorporchen Vienna, 1914 Cited by Snapper,<sup>10</sup> p 1
- 4 Mandl, F Arch f klin Chir., 143 245, 1926
- 5 Cope, O Clinics, 1 1168, 1943
- 6 Castleman, B and Mallory, T B Am J Path , 11 1, 1935
- 7 Thannhauser, S J Medicine, 23 105, 1944
- 8 Albright, F, Baird, P, Cope, O and Bloomberg, E Am J Med Sci, 187 49, 1934
- 9 Elsom, K A, Wood, F C. and Ravdin, I S Am J M Sc, 191 49, 1936
- 10 Snapper, I Medical Clinics on Bone Diseases New York, Interscience Publishers, 1943
- 11 Morelle, J and Beyerinck, C W Cited by Snapper,<sup>10</sup> p 69
- 12 Albright, F, Sulkowitch, H W and Bloomberg, E. Am J M Sci., 193 800, 1937
- 13 McLean, F C and Hastings, A B Am J M Sci, 189 601, 1935
- 14 Gutman, A B., Tyson, T L and Gutman, E B Arch Int Med., 57 379, 1936
- 15 Wilder, R M, Camp, J D, Robertson, H E. and Adams, M Proc Staff Meet., Mayo Clinic, 7 597, 1932
- 16 Barnay, J D and Sulkowitch, H W J Urol, 37 746, 1937
- 17 Downs, R S and Scott, V Arch Int. Med, 67 658, 1941
- 18 Cope, O Ann Surg, 114 706, 1941
- 19 Churchill, E. D and Cope, O Ann Surg., 104 9, 1936
- 20 Snell, A M and Mayo, C W Proc Staff Meet., the Mayo Clinic 11 633, 1936
- 21 Gentile, R J., Skinner, H L and Ashburn, L L Surgery, 10 793, 1941
- 22 McLean, F C J.A.M.A., 117 609, 1941

# THE RESTRICTION OF ACTIVITY IN CORONARY OCCLUSION WITH PARTICULAR REFERENCE TO THE EXTENT OF MYOCARDIAL INFARCTION

G N AAGAARD, M D.,\* AND C. J. WATSON, M D, F A C.P †

CORONARY occlusion commonly results in myocardial infarction. The classical clinical picture of agonizing substernal pain often radiating down the arms, ashen color, cold and clammy skin, reduced blood pressure, soft and muffled heart tones is well known and requires no further comment. Also well known are the common objective or collateral findings of myocardial infarction which include the following fever, leukocytosis, increased sedimentation rate, pericardial friction rub, and the characteristic electrocardiographic changes. In addition to these, attention has been called in recent years to the frequent finding of increased amounts of urobilinogen in the urine.<sup>1 2</sup>

It has been established that coronary occlusion does not always cause myocardial infarction. Blumgart and his co-workers<sup>3</sup> have shown in clinical and pathological studies, that one or more of the major coronary arteries may be occluded without gross or microscopic evidence of myocardial infarction at postmortem examination. Review of the histories often failed to reveal either previous angina of effort or attacks of chest pain resembling those usually associated with myocardial infarction. Blumgart believes that sufficient collateral circulation was present at the time that complete closure occurred to maintain an adequate blood supply and prevent infarction.

It is evident that coronary occlusion may be a serious event leading to myocardial infarction and death on the one hand, or a relatively benign episode with little or no infarction, and at times with little or no distress. Between these two extremes, there are a large number of cases in which the presence of an infarct is doubtful.

Since the amount of damage suffered by the myocardium following coronary occlusion may vary so markedly from case to case, it is obvious that no single plan of management is applicable in all cases. Restriction of activity is one of the major means employed in the treatment of coronary occlusion, hence the question often arises as to how much and how long the activity of the patient should be restricted. Strict bed rest for one to two months with as complete restriction of

---

From the Department of Medicine, University of Minnesota Hospitals, Minneapolis, Minnesota

\* Instructor in Medicine, University of Minnesota.

† Professor and Head Department of Medicine, University of Minnesota.

activity as possible for the first two weeks has been a common practice in the management of such cases. Recently Harrison<sup>4</sup> and Levine<sup>5</sup> have emphasized the fact that bed rest may actually be harmful to patients with cardiovascular disease if it is excessively prolonged.

The following cases of coronary occlusion illustrate some of its varying manifestations and afford an opportunity to consider its management from the standpoint of the presence or absence of an infarct.

#### CORONARY OCCLUSION WITH CONCLUSIVE COLLATERAL EVIDENCE OF MYOCARDIAL INFARCTION

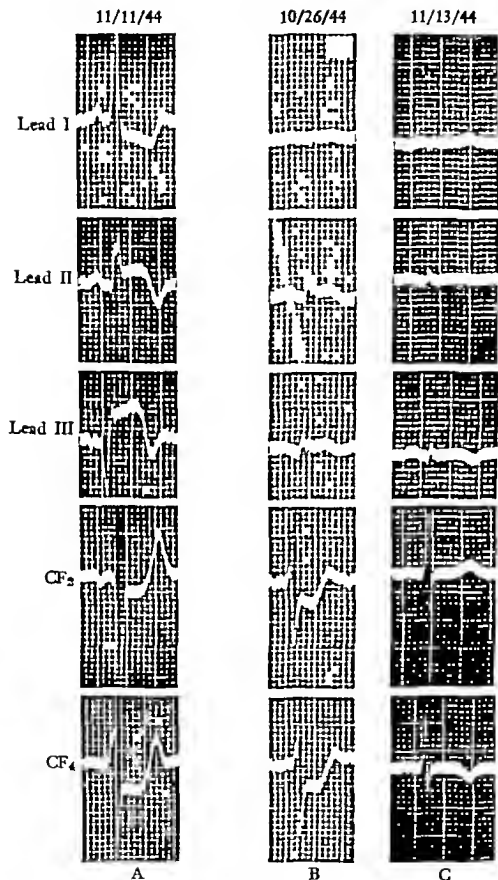
**CASE I—M P**, a 51 year old white woman, suffered an attack of substernal pain with radiation to both arms on November 2, 1944. The pain lasted several hours and then disappeared. It returned on November 4 and continued for two days when she was admitted to her local hospital. The pain continued despite bed rest. Temporary relief was obtained from nitroglycerin administered under the tongue. Because of the persistent pain she was admitted to the University of Minnesota Hospitals on November 11, 1944. Inquiry into her past health revealed that she had been found to have hypertension several years previously. Dyspnea and angina on effort had been present for several years.

Physical examination revealed the following pertinent findings: blood pressure 170/120, pulse 120 per minute, rhythm regular, temperature 99.6° F, lungs clear, heart tones soft, tic-tac rhythm. The temperature rose to 101° F on the day after admission and remained moderately elevated until November 20 when it became normal consistently.

The white blood count on admission was 24,250. The blood sedimentation rate (Westergren) recorded in millimeters in one hour was 65 on November 13, 93 on November 16, and 90 mm on November 21. The 2 to 4 P.M. urine Ehrlich value\* was 5.4 units on November 13 and had fallen to 1.8 EU on November 19. The electrocardiogram taken on November 11 (Fig 81A) was characteristic of posterior myocardial infarction. A pericardial friction rub was heard over the cardiac apex on the second hospital day. Her condition was serious for several days. She then improved and was symptom free on November 20, 1944.

*Comment*—This case exhibits the characteristic picture of coronary occlusion with myocardial infarction. All of the objective signs of infarction are present in significant degree. The magnitude of the leukocytosis, the prolonged serious state of the patient, and the widespread friction rub with a posterior myocardial infarction suggest that the infarcted area is large. Mallory<sup>6</sup> has shown that small infarcts may heal completely in five weeks but that large infarcts may take up to two months. This patient should be kept at absolute bed rest for two or three weeks and in bed for six to eight weeks. Only then should she be permitted to be up for short, increasing periods. If such activity is well tolerated, she may be permitted to walk about her room and then very gradually widen the sphere of her activities.

\* This is simply a quantitative measure of the urine Ehrlich reaction. Since this is chiefly due to urobilinogen, the values obtained are roughly correlated with the actual content of urobilinogen.<sup>7</sup> One Ehrlich unit is the amount of color produced in the Ehrlich reaction by 1 mg of crystalline urobilinogen. The upper limit of normal for the 2 to 4 P.M. urine sample probably should not exceed one unit.<sup>7</sup>



A

B

C

Fig 81—A, Electrocardiographic changes in Case I B, C, Electrocardiographic changes in Case II.

#### CORONARY OCCLUSION WITH MINOR OR QUESTIONABLE EVIDENCE OF INFARCTION

CASE II—M B., an 87 year old white woman awakened at 6 30 A.M. on October 27 1944 with marked dyspnea but no precordial pain. She had noticed slight dyspnea and palpitation on climbing stairs. She had never noted angina on effort.



Physical examination revealed the following pertinent findings. The patient was extremely dyspneic. Blood pressure was 110/70 and pulse 120 per minute. Bubbling râles were heard throughout the lungs. Heart tones were soft. Temperature was normal except for the third day when it rose briefly to 99.8° F.

The white blood cell count was below 10,000 except for a count of 11,350 per cu mm on October 29. At this time the neutrophils were 72 per cent. Sedimentation rate varied but slightly, being 29 mm in one hour on October 27 and going up to maximum value of 37 mm on November 11. The daily urine Ehrlich reaction was normal for seventeen days after the attack. An electrocardiogram on October 27 (Fig 81, B) showed changes typical of posterior myocardial infarction. Serial electrocardiograms showed progressive changes until November 13 (Fig 81, C), after which date no further changes occurred.

The patient obtained prompt relief from the initial dyspnea following  $\frac{1}{8}$  grain of morphine sulfate hypodermically. She was placed in an oxygen tent for two days and had no recurrence of symptoms. She was allowed to be up on the nineteenth day, and her activity was gradually increased. On January 25, 1945, she was feeling quite as well as prior to the attack.

*Comment*—This case presents several points which are worthy of mention. At no time did the patient complain of chest pain. Her attack was signaled by the sudden onset of symptoms of left heart failure. In this connection it may be noted that numerous cases of painless myocardial infarction have been recorded<sup>8, 9, 10, 11, 12</sup>. Atypical manifestations which are reported include sudden onset of dyspnea, cough or edema, sudden changes in cardiac rhythm, collapse or fainting, nausea and vomiting, central nervous system complaints, including vertigo, psychic disturbances, hemiparesis or coma. Although this case exhibited typical electrocardiographic findings of myocardial infarction, there was but very little other collateral evidence of necrosis of heart muscle. The symptoms were of very short duration, the temperature was elevated but once on the four-hour record, leukocytosis was minimal, and the sedimentation rate rose but insignificantly above the level shown shortly after the initial symptoms. Because of her age and the evidence which suggests that the infarct, if any, is small, the patient's activity should not be restricted too greatly nor too long.

CASE III—J J, a 56 year old white woman, noted the onset of substernal pain while sitting in church on November 12, 1944. She felt weak and noted profuse perspiration. The pain persisted until the following day, when she was admitted to the University of Minnesota Hospitals. She had first been told that she had hypertension two years previously. Exertional dyspnea and orthopnea had been present for several years. Angina on effort relieved by rest had been present for two years.

Physical examination revealed the following pertinent findings: blood pressure 200/98, pulse 70 per minute, temperature 98° F. Ocular fundi: A-V compression and moderate narrowing of the arterioles. The lungs were clear and heart tones were normal, but a soft systolic murmur was heard along the left sternal border. The temperature remained normal throughout.

The daily leukocyte count was never above 7600 per cu mm with uniformly normal differential counts. Sedimentation rate was as follows: November 13, 36 mm, November 17, 30 mm, November 20, 13 mm. The Ehrlich reaction of the

urine was normal on November 14, increased to 3.38 units two days later and had decreased to 1.8 units on November 20. An electrocardiogram on November 14 (Fig 87 A) revealed a negative T wave in Leads I and II and in the pre

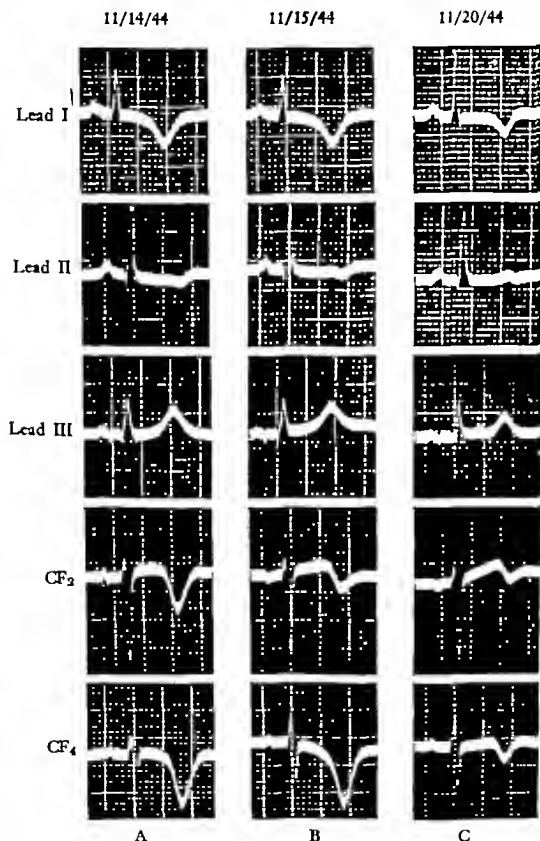


Fig 82—A, B, C, Electrocardiographic changes in Case III.

cordial leads, CF<sub>2</sub>, and CF<sub>4</sub>. There was no elevation of S-T. On the following day there was a slight change in the ST-T portion in CF<sub>2</sub> (Fig 82 B). On November 20, 1944, T had become upright in Leads II and CF<sub>2</sub> (Fig 87 C).

*Comment*—This patient also shows some of the objective evidence of myocardial infarction. Note the absence of fever and leukocytosis. Levy and his co-workers<sup>13</sup> found fever at some time during the course of cardiac infarction in 100 per cent of the cases they studied. The increased excretion of urobilinogen and the changing electrocardiogram are significant. It is difficult to evaluate the sedimentation rate in this case since it was slightly elevated on November 13, the day after the onset of symptoms. This is earlier than the peak usually occurs and suggests that this may not be due to the coronary occlusion. The absence of some of the collateral evidence of infarction suggests that the infarct is a small one. Such a patient can probably be safely lifted into a chair after the second week, especially if she tolerates poorly confinement to bed. Walking about the room can probably be permitted with relative safety during the fourth or fifth week.

CASE IV—C S., a 67 year old white man, was admitted to the University of Minnesota Hospitals on December 7, 1937. He had suffered substernal pain on effort, after meals and emotional stress, for two and one-half years. The attacks had become more frequent and were precipitated by very slight exertion. Rest and nitroglycerin gave relief. He was admitted to the hospital to see if anything more could be done to prevent these attacks.

Physical examination revealed the following pertinent findings: blood pressure was 140/90, and the pulse 80 per minute. The lungs were clear. Heart tones were normal, and no murmurs were heard.

The electrocardiogram (Fig 83, A) showed left axis deviation, widening and slurring or notching of QRS and what appears at first glance to be a Q wave in Lead III. There is, however, a small R wave preceding the downward deflection so it should probably be regarded as an S wave. It should be noted that the fourth lead in the electrocardiograms in this series was taken with the older technic in which the initial QRS deflection and the T wave are normally downward. Sedimentation rate was 18 mm in one hour. At 7:30 A.M., on the day after admission the patient suddenly collapsed in the bath tub and did not respond. Involuntary defecation occurred. The skin was cold and clammy and the blood pressure 120/64. Aminophylline, grains  $3\frac{3}{4}$ , was given intravenously. Shortly afterwards the patient responded normally, and normal color and skin temperature returned. An electrocardiogram (Fig 83, B) taken one hour after the episode shows elevation of S-T in Leads III and IV with T<sub>3</sub> positive instead of negative in the previous tracing. Depression of S-T in Leads I and II is also seen. A third tracing (Fig 83, C) taken three hours later reveals that these changes have disappeared and shows no significant variation from the first record. Tracings made on the next three days showed no change from the control record. An electrocardiogram taken December 13 showed elevation of S-T only in Lead IV. It is possible that this was taken during an episode of angina, but no definite information is available regarding that point.

Temperature and daily leukocyte counts remained normal. Urine urobilinogen was normal each day. The sedimentation rate varied from 8 to 20 mm in one hour except for a reading on December 10 when a value of 31 mm was obtained. The patient's condition remained the same as on entry, anginal attacks occurred after meals, on exertion, and after emotional stress related to telephone calls. Relief was obtained from nitroglycerin.

The patient was discharged from the hospital on December 18, 1937, at 3 P.M., feeling very well. That evening he became excited while making arrangements

to catch a train and had severe substernal pain. He was readmitted to the University Hospital at 10 p.m. He was restless and apprehensive, with a blood pressure of 130/90, pulse 120, and respiration 30 per minute. An electrocardiogram (Fig 83, D) taken after his readmission shows a rate of 136 per minute and

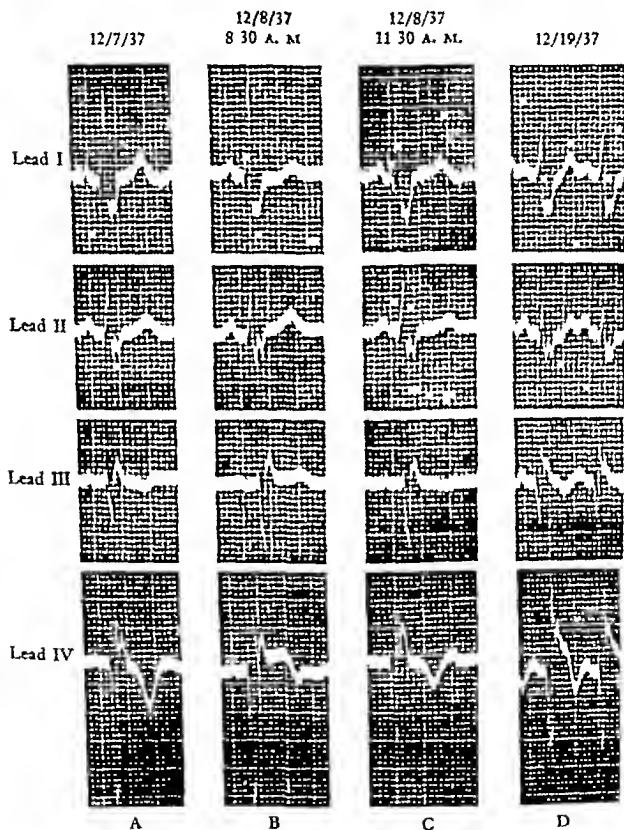


Fig 83—A, B, C, D, Electrocardiographic changes in Case IV

changes of S-T and T portions similar to that in Fig 83 B. The white blood cell count on December 19 was 14,200 per cu. mm. Despite complete bed rest and other therapeutic measures, the patient expired at 4 p.m. on December 19, 1937. Unfortunately permission for necropsy was denied.

*Comment*—The episode of unconsciousness and collapse noted above may represent another example of an atypical manifestation of coronary occlusion. The electrocardiogram shows changes suggestive of posterior myocardial infarction but these are very transient and disappear in three hours. Whether such electrocardiographic changes are due to myocardial infarction (necrosis) or to temporary myocardial ischemia without infarction is an important question. That myocardial ischemia produced by exercise or breathing a mixture of 10 per cent oxygen and 90 per cent nitrogen may cause S-T depression and T wave inversion is well known<sup>14 15</sup>. Less commonly, this may produce the Q-T pattern with S-T deviation usually considered typical of myocardial infarction<sup>16</sup>. The differentiation between myocardial infarction and temporary coronary insufficiency cannot be made by a single tracing. The length of time that the electrocardiographic changes are present is of value. If the pattern disappears and the tracing returns to the control pattern present before the attack within a period of forty-eight hours or less, the diagnosis of transitory myocardial ischemia is more likely. Collateral evidence of infarction must be sought. In this case none was present with the possible exception of the slight change in the sedimentation rate.

In retrospect, it is thought that somewhat more attention might have been given in this case to the changing electrocardiographic pattern, and the slight increase in sedimentation velocity. An autopsy was not permitted so no definite information is available as to the actual course of events. It is believed likely, however, that the patient suffered a new coronary occlusion on the day before death, and that the result would probably have been the same even if activity had been more restricted.

#### CORONARY OCCLUSION WITHOUT MYOCARDIAL INFARCTION

Blumgart and Schlesinger's studies have shown that coronary occlusion occurs not infrequently without resultant myocardial infarction. The importance of recognizing such an event when it occurs is obvious. During the period immediately following coronary occlusion, the degree of myocardial ischemia which results will depend on the amount of blood available through the preexisting collateral circulation, and the demand of the myocardium for oxygen which depends, of course, in large measure upon the activity of the patient. In experimental occlusion of the coronary arteries in dogs, it has been demonstrated that collateral circulation develops relatively slowly as compared with that developing after occlusion of such vessels as the femoral or carotid arteries<sup>17</sup>. A week or more may be required for adequate retrograde flow to develop in the dog's coronary arteries. Although such work cannot perhaps be applied directly to the problem in humans, it is likely that the development of coronary collateral circulation is even slower in man, as is evident from the slower rate of healing of infarcts in man as compared with dogs.<sup>6</sup>

It is obvious that the diagnosis of coronary occlusion without myocardial infarction cannot be proved during life. This would require a blind faith in the lack of collateral evidence of infarction, such as already referred to. While it is believed that in the absence of such evidence the presence of an infarct may be seriously doubted, it is recognized that further clinical and pathologic correlations are needed before one can employ this collateral evidence in an absolute manner.

The diagnosis of recent coronary occlusion without infarction must be considered under the following circumstances: (1) prolonged substernal pain characteristic of coronary occlusion without ensuing collateral evidence of infarction, (2) the *sudden* or *rapid* onset of the typical syndrome of angina pectoris, i.e., pain on effort, emotional stress, or after meals, or of symptoms of congestive heart failure, nausea and vomiting, syncope, collapse, and the central nervous manifestations noted above without any other satisfactory explanation, (3) sudden or rapid increase in the frequency or severity of anginal attacks in a patient who has previously suffered with angina pectoris. Any of these clinical pictures should suggest the possibility of coronary occlusion.

**CASE V**—E. H., a 55 year old white woman, had enjoyed good health until July 11, 1940, at 1:30 P.M., when she suddenly experienced an attack of severe, viselike pain in the substernal area. There was some radiation to the interscapular area. With the pain she noted dyspnea, orthopnea, faintness, and a sense of impending death. She vomited once without relief from the pain. When she was seen at her home two hours after the onset, the pain was still very intense. Physical examination revealed the following pertinent findings: the patient was obviously in acute distress, the skin had an ashen pallor with slight but definite cyanosis of the lips and extremities. Blood pressure was 110/90, and pulse 58 per minute and of poor quality. Heart rhythm was regular. Cardiac tones were muffled and distant.

The patient was admitted to the University of Minnesota Hospitals by ambulance a few hours after the onset. An electrocardiogram showed a small Q wave in Lead III; there was no displacement of the S-T junction and the T waves were upright in all four leads. Morphine sulfate was given subcutaneously when the patient was seen at home and provided relief from this pain. Because of cyanosis, the patient was placed in an oxygen tent immediately after her entry to the hospital ward. Her color improved immediately and she did not complain of further pain during her hospital stay.

The patient's temperature was consistently normal save for one recording of 99° F. on the fourth day of her illness. The white blood cell count was 5000 and 6000 per cu. mm. on two occasions. Sedimentation rate was 12 mm. in one hour on the fourth hospital day. Ehrlich reactions of the urine, unfortunately, were not recorded. A second electrocardiogram showed no change from the original tracing.

The patient was completely free of symptoms after the first few hours of her hospital stay and was discharged from the hospital on July 15, 1940, the fourth day after the attack, with instructions to limit her activities at home. Attempts to obtain further information about this patient were unsuccessful.

*Comment*—Although exact proof of coronary occlusion is lacking, the onset and character of the attack was most suggestive. The absence of any history of gastrointestinal complaints, pulmonary disease, etc., is of additional help in making a presumptive diagnosis of coronary occlusion. The absence of collateral evidence of myocardial infarction supports the view that this is an instance of coronary occlusion without infarction. No one could deny that coronary spasm might produce such a clinical picture, although it would seem wiser, here, to make a diagnosis of occlusion without infarction and treat the case as one of coronary occlusion. Ten days to two weeks of bed rest followed by a similar period of confinement in one room or at least on one floor, is believed advisable in such instances. This would give time for additional collateral circulation to develop under optimal conditions of rest for the heart.

CASE VI—E. B., a 53 year old white man, was admitted to the University of Minnesota Hospitals on November 23, 1939. He stated that five years previously he had had a sudden attack of oppressive pain in the precordial and substernal areas, with radiation down his left arm. The pain had lasted several hours and he felt so weak and incapacitated that he had stayed home from work for several days but had not called a doctor to see him. Following this he had noted that exertion which had formerly caused no distress now caused dyspnea. In fact, because of this shortness of breath, he had found it necessary to give up golf.

On the day before admission, while driving his car in the evening, the patient noted the sudden onset of substernal pain similar to that described above. He was able to drive home by himself. The pain lasted four hours and was not relieved by an enema. He went to work on the morning of admission, but while at his desk he noted the sudden onset of substernal soreness and heaviness and felt as if he would collapse. A doctor was called and the patient was taken to the hospital.

Examination at the time of admission revealed the following pertinent findings. Patient was pale, and slight cyanosis of the lips was present. Blood pressure was 110/90 and pulse 60 per minute, weak and regular. Heart tones were soft and distant. No murmurs were heard. Crepitant râles were present at both bases of the lungs posteriorly. An electrocardiogram was taken on admission and was normal. White blood cell count was 8600.

During his four-day hospital stay, the patient's temperature was always normal. Treatment consisted of aminophylline 0.5 gm given intravenously at the time of entry, and sedation. His substernal discomfort disappeared after he had been in the hospital a few hours. This patient had no further pain or dyspnea during a subsequent two-year period.

*Comment*—It is entirely possible that this patient had an occlusion of one of his coronary arteries in the attack which occurred five years before he was observed in this hospital. The diagnosis of coronary occlusion without myocardial infarction for the present admission is probably justified because of the characteristic subjective manifestations and the lack of collateral evidence of infarction, although this was not studied in as much detail as is desirable. In this case also, it would perhaps have been better to err on the side of greater restriction of activity for a longer period.

CASE VII—R. H., a 48 year old white man, was first seen in the Out Patient Department of the University of Minnesota Hospitals on July 23 1941. He stated that he had enjoyed good health and normal activities until exactly two weeks previously. On that day he had noticed that walking up a small hill which he climbed each day on his way to the streetcar caused an oppressive type of pain in the substernal area. He also noted for the first time on that same day that climbing stairs also caused the same type of distress. The discomfort would disappear if he remained absolutely quiet for five minutes as soon as the pain appeared.

Examination ten days after the onset of angina showed nothing of significance. The blood pressure was 134/84. The heart was normal in size and contour and no murmurs or abnormal sounds were heard. The pulse was 86 per minute and regular. Fluoroscopy confirmed the finding that the heart was normal in size and showed nothing else of significance. An electrocardiogram was within normal limits. The leukocyte count and temperature were normal. Nitroglycerin, grain 1/100 when given under the tongue gave relief from the symptoms. The patient remained at home for two weeks during which time he did not climb stairs or engage in anything but the mildest activity. At the end of that time he was able to engage in his normal activities again without distress. It was possible to follow this patient for one year during which he complained of nothing more than mild dyspnea on exertion.

*Comment*—Again no proof can be offered as to the exact diagnosis. The sudden onset of angina of effort in a patient previously free of cardiac symptoms suggests reduced coronary flow. In the absence of other causes of myocardial ischemia such as acute anemia, shock, tachycardia, and severe toxic states, a presumptive diagnosis of coronary occlusion without myocardial infarction is in order. Without causing undue alarm, the patient's cooperation should be obtained in a program of moderate restriction of activity.

#### SUMMARY AND CONCLUSIONS

1 Collateral evidence of myocardial infarction should be sought in all instances where the diagnosis of coronary occlusion is entertained. This evidence includes the following: (a) fever, (b) leukocytosis, (c) increased sedimentation velocity and (d) increased Ehrlich reaction in the urine (urobilinogen). Serial electrocardiographic changes are, of course, of the utmost importance, but it is believed that changes may occur in some cases without actual necrosis of heart muscle.

2 In instances where conclusive collateral evidence of infarction is obtained, bed rest is advisable for at least six weeks. Where such evidence is lacking or questionable, it is believed that restricted activity out of bed may be permitted after a shorter period of time. This assumes that a daily search for the collateral evidence has been made for two weeks following the attack.

#### BIBLIOGRAPHY

- 1 (a) Watson, C. J., Arch. Int. Med., 59 206, 1937.  
(b) Watson, C. J., New England J. Med., 227 705 Nov. 5 1942.
2. Head, D. P., Unpublished data.



- 3 Blumgart, H L., Schlesinger, M J and Davis, D *Am Heart J*, 19 1, 1940
- 4 Harrison, T R. *J A M A*, 125 1075 (Aug 19), 1944
- 5 Levine, S A *J.A.M.A.*, 126 80 (Sept 9) 1944
- 6 Mallory, G K., White, P D and Salcedo-Salgar, J *Am Heart J.*, 18 647, 1939
- 7 Watson, C J *Am J Clin Path*, in press
- 8 Pollard, H M and Harvill, T H *Am J M Sc*, 199 628, 1940
- 9 Stroud, W D and Wagner, J A *Ann. Int. Med*, 15 18, 1941
- 10 Bean, W B and Read, C T *Am Heart J*, 23.362, 1942
- 11 Stroud, W D and Wagner, J A *Pennsylvania M J.*, 45 590 (March) 1942
- 12 Strong, G F *Canad M A J*, 47 460 (Nov ) 1942
- 13 Shillito, F H., Chamberlain, F L and Levy, R L *J.A.M.A.*, 118 779, 1942
- 14 Feil, H *Blood, Heart and Circulation Science Press*, 1940, p 163
- 15 Levy, R L, Bruenn, H G and Russell, J N G *Am J M Sci.*, 197 241, 1939
- 16 Katz, L N *Philadelphia, Lea & Febiger*, 1941
- 17 Eckstein, R W., Gregg, D E. and Pritchard, W H *Am J Physiol.*, 132 351, 1941

## RECENT ADVANCES IN PHARMACOLOGY

EDGAR W. WARREN, M.D.,\* AND THOMAS FINDLEY, M.D., F.A.C.P.†

ANY review such as this must necessarily be incomplete. In the present instance, omission of a discussion of the sulfonamides and penicillin is intentional for obvious reasons. The vitamins have also not been included for they are much talked about, and we have not felt qualified to write about the remedies for tropical diseases. The unintentional omissions are due to ignorance and neglect, in self-defense it should be stated that the most important announcements are often made from obscure sources. We have tried to make this review of immediate use to the practitioner.

### CENTRAL NERVOUS SYSTEM

**Demerol**—Since 1939 intensive studies<sup>1-7</sup> have been made on the pharmacologic and clinical properties of the ethyl ester of 1-methyl-4-phenyl-piperidine-4-carboxylic acid (demerol), a synthetic product related to morphine and atropine. It combines the analgesic effects of the former drug with the spasmolytic actions of the latter.

Clinically,<sup>8-17</sup> demerol is useful in relieving conditions accompanied by *smooth muscle spasm*—biliary or ureteral colic, bronchial asthma, abdominal cramps, angina pectoris, arterial thrombosis or embolism, labor pains and hiccups. The effect of 100 mg. of demerol on the pain perception threshold is roughly equivalent to that produced by 15 mg. of morphine sulfate.<sup>18</sup>

*Side reactions* of a moderate degree occur in about 25 per cent of bed patients, but giddiness, pallor, sweating, blurring of vision and nausea develop in 50 per cent of ambulatory patients. This drug has been recommended,<sup>11</sup> therefore, mainly for bedridden patients in doses of 50 to 100 mg. every three to four hours although much larger doses have been safely given. It is more effective when given intramuscularly although the rapidity of action after oral administration is but slightly delayed. It should never be given intravenously.

*Toxic effects*<sup>8</sup> may simulate poisoning by atropine or morphine. Thus, there may be extreme mydriasis, dryness of the mouth, tachycardia, hallucinations, disorientation, muscular twitching and occasionally slight rise in blood pressure, pulse rate and temperature. Comparable to any drug capable of producing euphoria, demerol may induce

---

From the Division of Internal Medicine, Ochsner Clinic and the Department of Medicine, Tulane University School of Medicine, New Orleans.

Assistant in Division of Internal Medicine, Ochsner Clinic. Instructor in Medicine, Tulane University School of Medicine.

†Director, Division of Internal Medicine, Ochsner Clinic. Assistant Professor of Clinical Medicine, Tulane University School of Medicine.

addiction, although the tendency is much less than that of morphine<sup>8 19, 20, 21</sup> It has been clearly shown<sup>22</sup> that on withdrawal of the drug after thirty to sixty days' usage, the usual symptoms of yawning, lacrimation, rhinorrhea, sweating, dilated pupils, insomnia and aching legs may rapidly appear

In the search for morphine substitutes, Jones and Chapman<sup>23</sup> have reported recently on the comparative analgesic effect of morphine sulfate and *monoacetylmorphine* They felt that a given dose of the latter was four times as effective as a similar dose of morphine sulfate—not only regarding the maximum threshold to pain but also as to duration of action Further, monoacetylmorphine produced less toxic reactions such as nausea and vomiting However, euphoria of moderate degree was also more frequently noted They suggest that these two actions unfortunately may lead to more frequent addiction

**Barbiturates**—The most important extension of the use of the barbiturates has been in relation to *war casualties of a psychiatric nature*<sup>24 25</sup> Properly employed as one feature of a highly specialized technic, the drug seems to release cortical inhibitions and permits mental catharsis Soluble pentothal sodium has also been advocated<sup>26</sup> for the control of neurogenic hyperthermia which follows injury to the hypothalamus

*Toxic reactions* continue to occur In a case of exfoliative dermatitis the daily administration of 500 mg of nicotinic acid seemed efficacious<sup>27</sup> The treatment of respiratory failure with such analeptics as picrotoxin, metrazol and coramine has been recently reviewed by Hazelton<sup>28</sup> After all these measures had failed in one case, sodium succinate (22 gm in a 10 per cent solution) was administered intravenously over a period of five hours with recovery<sup>29</sup>

**Motion Sickness**—For obvious reasons much interest has naturally centered about the prevention and treatment of seasickness and airsickness For the prevention of the former, a careful study<sup>30</sup> has suggested that *hyoscine* in oral doses of 0.6 mg is more effective than any other drug It produced some dryness of the mouth, diminution of sweating and elevation of body temperature, but apparently had no effect on infantry marksmanship It is contraindicated in cases in which heat stroke might develop *Benzedrine* has also been advocated for the prevention of motion sickness

**Epilepsy**—Waelsch and Price<sup>31</sup> report on the effectiveness of *glutamic acid* in the treatment of petit mal and other epileptic equivalents It was originally thought that the efficacy of the drug was due to its capacity for producing acidosis but these workers have apparently abandoned that idea and now suggest that amino acid deficiency may influence cortical activity This drug apparently does not influence gross seizures but is effective in controlling those episodes associated with slow wave activity in the electroencephalogram Given in doses of 12 gm daily it was well tolerated, seemed to increase the vigor of the patients and produced considerable reduction in the psychomotor seizures

## LOCAL ANESTHESIA

**Procaine Hydrochloride**—Continued efforts have been made to find a less toxic regional anesthetic than procaine. An isomer of the latter, *monocaine*, has been synthesized and found<sup>32</sup> to be equal in efficacy and toxicity, though slightly more irritating to the local tissues. *Monocaine* has the advantage of being more stable at room temperature and to light. At first *monocaine* was thought to have a greater pressor action but this has been disproved, nor does it potentiate the action of epinephrine. Other related drugs, such as octocaine and eucupin have also been brought forward but with no convincing evidence of their superiority over procaine.

It may not be generally known that procaine is a derivative of *p*-amino-benzoic acid, which inhibits the action of the sulfonamides. It has been clearly shown<sup>33</sup> that procaine will prevent the proper action of sulfonamides in contaminated wounds, as procaine breaks down into *p* amino-benzoic acid. Therefore, the rationale of using mixtures of *sulfonamides* with *procaine* seems erroneous. Recently, it has been suggested<sup>34</sup> that procaine be combined with a local antiseptic such as rivanol, in the treatment of painful purulent wounds.

The *indications* for the use of procaine have been widely extended. It is commonly used as a temporary or permanent substitute for sympathectomy.<sup>35</sup> Local infiltrations are employed in the management of nonarticular rheumatism.<sup>36</sup> Paravertebral block is advocated for the treatment of herpes zoster.<sup>37</sup> and intercostal injection for the relief of postoperative atelectasis.<sup>38, 39</sup>

It must be remembered that procaine and its associates are convulsants. Prophylactically therefore, one might very well employ a judicious amount of a barbiturate. Should convulsions occur a calcium salt may be given intravenously. calcium levulinate, gluconate and chloride are decreasingly effective in the order listed. From 3 to 6 cc of per cent sodium is also an effective anticonvulsant. Should syncope occur artificial respiration or the use of 5 per cent carbon dioxide and 95 per cent oxygen is indicated.

**Bromsalizol**.—Lee, Macht and Pierpont<sup>40</sup> report that a 4 per cent solution of mono-brom-hydroxyl-benzyl alcohol in peanut oil (Bromsalizol Hynson Westcott & Dunning) produces prolonged paralysis after sympathetic block, an obvious advantage. We have employed it several times, however for injection of the stellate ganglion and have been unable to see that the Horner's syndrome lasted appreciably longer than after the injection of 1 per cent procaine.

## AUTONOMIC NERVOUS SYSTEM

**Sympathomimetic Drugs**—In addition to epinephrine and the familiar ephedrine and amphetamine (benzedrine) several other compounds possessing the ability to mimic stimulation of the sympathetic nervous

system should be mentioned. It is believed that the activity of the pressor amines may be due to their ability to delay or prevent the oxidation of epinephrine, having chemically similar compositions, they may compete with epinephrine for available amine oxidase and thus interfere with its enzymatic destruction. Some of them, however, have special actions which make them clinically useful.

*Ephedrine*—Kittredge and Brown<sup>41</sup> report the successful treatment of enuresis in a dosage of 50 mg orally at bedtime. They say that even children are not kept awake by this amount.

*Neosynephrin Hydrochloride*—Differing from epinephrine only in possessing one rather than two hydroxyl groups on the benzene nucleus, neosynephrin is such a stable compound that it raises blood pressure when taken by mouth in doses of about 50 mg. In parenteral doses of 5 mg or less the resulting hypertension may persist for two hours. Like other vasoconstrictors it is contraindicated in shock but is used to sustain blood pressure after the production of spinal anesthesia and has been occasionally useful in orthostatic hypertension. In watery solution or in jelly it is applied topically in the same manner as ephedrine or amphetamine.

*Kephrine Hydrochloride*—As the hydrochloride, kephrine is used only locally to arrest capillary bleeding. Bandages are impregnated with it and it is also marketed in powder form and as rectal suppositories.

*Propadrine Hydrochloride*—This drug, closely related to ephedrine, is less likely to cause unpleasant central nervous system stimulation and is regarded as a more potent vasoconstrictor. As a spray or jelly it is used for shrinking nasal mucosa and has recently become popular as a remedy for coryza when taken orally in capsules of 25 or 50 mg.

*Racephedrine Hydrochloride* (d-1-ephedrine) has the same action, dosage and usage as ordinary ephedrine, which is the levo-isomer. It has no known advantages over the latter drug.

*Paredrine* (p-hydroxy- $\alpha$ -methyl-phenyl-ethylamine) is closely related to tyramine and amphetamine. It is more stable than epinephrine and possesses a stronger pressor action. It has practically no effect on the central nervous system, gastrointestinal tract or bronchial musculature. In doses ranging from 5 mg intravenously to 50 mg orally it stimulates the myocardium and causes sustained hypertension. These effects have provoked unusual interest because they are apparently unaccompanied by local vasoconstriction or diminished blood flow through the skin. Altschule and Iglauer<sup>42, 43</sup> found that the drug causes a striking increase in venous pressure. No definite statement can be made but it is possible that the hypertension is caused by a predominant venoconstriction. Paredrine is also a useful mydriatic in dilutions of 1 to 3 per cent.

*Paredrinol* (veritol,  $\beta$ -[p-oxyphenyl] isopropyl-methylamine) is chemically similar to, but perhaps a little less potent than paredrine, and its actions are probably the same. Stead and Kunkel<sup>44</sup> thought the pressor action due to (a) constriction of minute peripheral vessels, (b) increased venous pressure or (c) both. Kunkel, Stead and Weiss<sup>45</sup> found that it could prevent the postural syncope observed in normal persons under the influence of sodium nitrite and thought the drug might be useful in treating those vascular crises caused by diminished muscle tone and the pooling of venous blood. Ranges and Bradley<sup>46</sup> say that paredrinol may increase venous tone but that its primary action is that of peripheral vasoconstriction.

*D-desoxyephedrine Hydrochloride* is now receiving attention as a central nervous system stimulant in the treatment of narcolepsy, reactive depression and general fatigue. The literature has been reviewed by Ivy and Goetzl.<sup>47</sup> Recom-

mended clinical doses (2.5 mg tablets) are smaller than those of benzedrine but no definite advantages have been demonstrated.<sup>48</sup>  
*Tumaine Sulfate* (2-aminoheptane sulfate Lilly) in aqueous solution is used to reduce nasal congestion

**Parasympathomimetic Drugs.**—*Furmethide*—Furfuryl-thimethyl-ammonium iodide (Furmethide, Smith, Kline and French Laboratories, Inc.) is a parasympathomimetic drug with a strong action on the bladder. Beaser, Lipton and Altschule,<sup>49</sup> after a careful study of the drug, say that it has certain obvious advantages over mecholyl or doryl for the urologist. In doses adequate to cause contraction of the bladder (approximately 10 mg subcutaneously), it produces sweating, salivation, tachycardia and flushing but little or no effect on blood pressure, the gastrointestinal tract or the bronchial musculature. The oral doses of 30 mg cause only sweating and increased bladder tone. Obviously, the drug should not be used in the presence of obstruction of the neck of the bladder but is claimed to be useful in atonic conditions. It has been used in preference to pilocarpine for demonstrating areas of anhydrosis.<sup>50</sup>

#### NEUROMUSCULAR APPARATUS

**Myasthenia Gravis**—The asthenia in this curious disease is due to defective transmission of stimuli from nerve ending to muscle cell. The occasionally remarkable improvement which follows thymectomy forms the basis for a theory which states that a diseased thymus elaborates a curare-like poison. No such secretion has actually been isolated but Wilson and Stoner<sup>51</sup> report that the serum of patients with the disease, unlike that of normal persons, blocks neuromuscular transmission in frog nerve-muscle preparations. Torda and Wolff,<sup>52</sup> on the other hand, produced evidence which suggests that the fundamental defect consists of inadequate synthesis of acetylcholine, and not in failure of the myoneural apparatus or in abnormal muscle metabolism. In any event, a number of reasonably effective drugs are available for treatment.

*Neostigmine* is the drug of choice because it prevents cholinesterase from destroying acetylcholine. Viets<sup>53</sup> seems to regard myasthenia gravis as a deficiency disease, for he says that neostigmine constitutes a form of substitution therapy. The dosage must be large and should be varied to meet the individual patient's needs from day to day. A tablet of neostigmine bromide (U.S.P.) contains 15 mg and the average daily maintenance dose for 45 ambulatory patients was 163.5 mg some required as much as 375 mg daily. Ephedrine, potassium salts, guanidine and other drugs were regarded as auxiliary measures and not often needed. In severe relapse, neostigmine methylsulfate must be given parenterally. Viets has used as much as 25 mg intramuscularly or 3 mg intravenously in twenty-four hours.  
Wilson and Stoner<sup>54</sup> however, regard ephedrine as a useful adjunct

As much as 50 mg of ephedrine sulfate three times daily may be added to the neostigmine schedule

Bennett and Cash<sup>55</sup> have pointed out that the intramuscular injection of 1 mg or so of neostigmine methylsulfate as a diagnostic test for myasthenia gravis is reliable in only about two thirds of the cases because it may fail to induce unmistakable increase in muscle power. They think that patients with this disease are abnormally sensitive to curare because their serum contains an excess of curare-like material. Normal persons react only slightly to the intramuscular injection of 0.1 mg for each kilogram of body weight of curare, but patients with myasthenia gravis exhibit definite aggravation of muscle weakness, particularly of the extraocular muscles, after a dosage of one twentieth of this amount. They allow the action to proceed for two or three minutes and terminate it by the intravenous administration of neostigmine (1.5 mg) and atropine sulfate (0.6 mg).

*Quinine* may also be used as a diagnostic procedure, although the dosage and reliability apparently have not been well established. Harvey<sup>56</sup> has shown that it accentuates the symptoms of myasthenia gravis and relieves those of myotonia congenita because of its curare-like action. Quinine has been advocated also for the treatment of spasmodic torticollis, myotonia atrophica, paramyoclonus multiplex, the nocturnal leg cramps seen so often in elderly people and other similar conditions.

The rationale for the use of other drugs in myasthenia gravis is perhaps less well understood. *Glycine* has largely been abandoned. *Gumidine*, first advocated by Minot, Dodd and Riven,<sup>57</sup> has not been shown to have any special advantages. Its mode of action is unknown but it may sensitize skeletal muscles to acetylcholine. *Potassium* has also been used because it is known to facilitate transmission of nerve impulses. If large doses of neostigmine are given parenterally, it is sometimes useful to administer atropine simultaneously in order to eliminate undesirable side effects, the action of acetylcholine on voluntary muscle is not abolished by atropine.

**Cataplexy**—This paroxysmal inhibition of skeletal muscle, which appears to be initiated by sudden changes in mood, particularly laughter, is related to familial periodic paralysis. Dynes<sup>58</sup> reports its successful control by the oral administration of *potassium chloride* in doses of about 5 gm daily.

**Familial Periodic Paralysis**—The concentration of serum potassium is low during the attack and potassium salts cure the weakness.<sup>59</sup> Wolf<sup>60</sup> advocates the use of *thyroid*; he makes the astonishing claim that an oral dose of thyroid will alleviate an attack in from ten to thirty minutes and that it is often more effective than potassium.

**Fasciculation**—Neostigmine in adequate doses will produce coarse fibrillary muscle twitchings in normal persons and in patients with all muscular disorders except myasthenia gravis. Such fibrillations or fasciculations are not abolished by spinal anesthesia or peripheral nerve

block Forster and Alpers<sup>61</sup> review the literature and claim that these abnormal movements originate at the myoneural junction because they are increased by neostigmine, abolished by curare and not exaggerated by acetylcholine.

**Other Uses for Neostigmine**—Kabat and Knapp<sup>62</sup> advocate the use of neostigmine for the reduction of muscle spasm in *acute anterior poliomyelitis*. They have shown that this muscle spasm is temporarily relieved by spinal anesthesia and claim that neostigmine acts by inhibiting the spinal cord centers for proprioceptive reflexes. Trommer and Cohen<sup>63</sup> have accepted this idea and applied it to the treatment of *rheumatoid arthritis*. They gave 1 or 2 cc. of neostigmine methylsulfate with 0.6 mg. of atropine sulfate subcutaneously three or four times a week, and also gave 15 or 30 mg. of neostigmine bromide three times daily by mouth. This idea should be accepted cautiously because little is known about the action of neostigmine on the spinal cord and one would expect it to increase muscle tone rather than decrease it.

**Other Uses for Curare**—This material is available under the trade name of Intocostrene (E. R. Squibb & Sons). Its use in *tetanus* is not new but Cullen,<sup>64</sup> who has utilized it recently, claims that the parenteral administration of about 0.1 mg. for each kilogram of body weight will produce muscle relaxation for about three hours. The drug may be given intravenously or intramuscularly. It has also been used to facilitate muscle relaxation during *general anesthesia*. Cullen<sup>64</sup> and Baird and Adams<sup>65</sup> have reported favorable results. Pronounced respiratory depression has occurred frequently, however, and the drug has not been generally accepted by general surgeons. It is widely employed for *prevention of fractures during shock therapy* for mental disorders.<sup>66</sup>

## HEART AND CIRCULATION

**Cardiac Glucosides.**—Preparations of digitalis leaf present some obvious disadvantages and the search for satisfactorily pure crystalline glucosides continues. It is not claimed that these present any therapeutic properties not exhibited by the crude drug, but they do not deteriorate, they are more completely absorbed from the intestinal tract and their dosage may be expressed in terms of actual weight rather than as biologic (cat or frog) units. With them, the practice of digitalizing patients rapidly by either the oral or intravenous route is becoming more popular. Attention is also being paid to materials isolated from the leaf of *Digitalis lanata* as well as from the more familiar *Digitalis purpurea*.

Available preparations of partially purified glucosides are

1 *Digilanid*—Digilanid is a mixture of the isomorphous crystallized glucosides A, B and C from the leaves of *Digitalis lanata* in their naturally occurring proportions. This preparation seems needlessly complex and has not attained great popularity.

2 *Digitoxin* (*Digitaline Nativelle*—Fougere *Pourodigin*—Wyeth)—Digitoxin



is obtained by hydrolysis of both varieties of leaf but the commercial preparation is made from the *purpurea* plant. Its action is, of course, similar to that of *digitalis* but full effect may be obtained by the oral administration of only 1.25 to 1.5 mg, given in fractional doses of 0.5 mg at intervals of from four to six hours. Gold and his co-workers<sup>67</sup> found that patients could be quickly and fully digitalized by giving a single dose of about 1.25 mg either orally or intravenously, an observation which proved almost complete intestinal absorption in contrast to the crude preparations. The toxic dose, as for other glucosides, was about twice the therapeutic. The usual maintenance dose is 0.1 or 0.2 mg daily.

3 *Lanatoside C (Cedilanid, Sandoz)*—This glucoside is found only in the *Digitalis lanata* leaf. One of the first clinical studies was made by Fahr and Ladue,<sup>68</sup> who felt that the optimum intravenous dose was 8 cc (16 mg). Others<sup>69, 70, 71</sup> have shown that this dosage will usually reduce the ventricular rate of patients with auricular fibrillation to a normal level in three to four hours with no evidence of toxicity, but we have felt that this lack of toxicity is more apparent than real and are in the habit of reinforcing the intravenous procedure immediately by giving 0.1 gm of the powdered *purpurea* leaf orally two or three times daily until the patient has been unquestionably controlled. Rapid digitalization with cedilanid may also be achieved orally by giving 8 mg in tablet form. The recommended oral maintenance dose is 0.5 mg three times daily but we feel that this is often inadequate, we furthermore see no advantage in using pure glucosides for this purpose and have returned to the powdered leaf for continued treatment. We are enthusiastic, however, about the intravenous use of cedilanid and frequently employ it in ambulatory patients as it simplifies treatment considerably. It comes in 4-cc ampules, each cubic centimeter containing 0.2 mg.

4 *Digoxin* (Burroughs-Wellcome)—This drug is obtained from the hydrolysis of lanatoside C. We have had no experience with it but see no reason why it should not be a satisfactory product. Schwab<sup>72</sup> rapidly digitalized patients by the intravenous injection of 1.5 mg followed in six hours by 0.5 mg, only slightly slower clinical responses were obtained by the oral administration of 2.0 mg (a single dose) followed six hours later by 0.5 mg. This shows that intestinal absorption is rapid and almost complete. Maintenance was difficult because of rapid excretion and frequently required 1 mg a day or more.

5 *Ouabain*—A glucoside isolated from *Strophanthus gratus* is suitable for parenteral use only. In undigitalized patients the maximum intravenous dose is probably 0.5 mg in twenty-four hours. Eichna and Taube<sup>73</sup> assayed several glucosides clinically by giving them intravenously in equal gram-molecular doses to the same patient under fairly standard conditions and rate them according to speed of action in the following order—ouabain, digoxin, lanatoside C and digitaline nativelle. The differences are not great, however. Eichna and Taube<sup>74</sup> gave single intravenous injections of ouabain or digoxin to patients with congestive heart failure and observed that the initial measurable response was a fall in venous pressure.

*Synthetic Glucosides*—Chen and his associates<sup>75</sup> have prepared an interesting series of synthetic glucosides but the work has probably not reached the stage of clinical trial.

**Diuretics**—Combinations of mercury and theophylline are now available for oral use as salyrgan-theophylline tablets (Winthrop Chemical Co., Inc.) and mercupurin tablets (Campbell Products, Inc.). They are regarded as not entirely free from toxic properties but suitable for patients who do not require drastic and prompt diuresis.<sup>76, 77</sup> Their action may be enhanced by simultaneous administration of large doses

(8 to 12 gm) of ammonium chloride\* daily. Treatment may be begun with one tablet three times daily for four days, but this amount may be doubled or a single dose of five tablets may be given if more rapid diuresis is required. If no diuresis results, the attempt should be abandoned as mercury retention and poisoning may occur. Nausea, vomiting and mild diarrhea frequently occur. The reactions (some of them instantly fatal) which rarely follow the intravenous administration of mercurial diuretics have been reviewed by Wexler and Ellis<sup>78</sup>. The fatal ones are evidently due to cardiac arrest but in comparison with the number of injections given are extremely rare. Digitalis intoxication may occur if edema fluid is mobilized too rapidly.

**Rheumatic Fever**—Coburn<sup>79</sup> in a report which covers a period of two years' observation showed that in twenty patients in whom a blood salicylate level of 259 to 400 gamma for each cubic centimeter was maintained by daily intravenous injection of *sodium salicylate*, there was a prompt subsidence of activity in the rheumatic joints and a rapid return of the sedimentation rate to normal, but that in twenty patients with levels below 250 gamma, activity persisted. Valvular heart disease did not develop in any of the thirty-eight patients given at least 10 gm of sodium salicylate daily. On the other hand, twenty-one of sixty-three rheumatic patients given smaller doses exhibited signs of valvular disease.

A recent report by Smull, Wegria and Leland<sup>80</sup> indicates that the administration of sodium bicarbonate with salicylates in rheumatic fever may prevent the establishment of a satisfactorily high serum salicylate level.

Important studies by the Army<sup>81</sup> and Navy<sup>81a</sup> have demonstrated a dramatic reduction in the incidence of hemolytic streptococcic infections, rheumatic fever and respiratory infections as a result of the prophylactic use of 0.5 to 1.0 gm of *sulfadiazine* daily. In a large combined series the incidence of toxic reactions was almost negligible, and no evidence of mass sensitization has yet appeared.

**Subacute Bacterial Endocarditis**.—Neither the sulfonamides nor the anticoagulants alone or in combination have produced any striking reduction in the mortality rate of this disease. Earlier reports on penicillin were likewise disappointing, but it is hoped that the employment of larger doses may prove helpful. A recent report looks promising.\*

**Angina Pectoris**.—Levine<sup>82</sup> reports that testosterone propionate has no useful action in angina pectoris, contrary to earlier enthusiastic reports.

**Hypertension**.—The literature is full of reports praising alleged hypotensive drugs, particularly the sulfocyanates, but all of the recent, well controlled studies<sup>83-86</sup> reveal failure to demonstrate any useful property. Even vitamin A has acquired its supporters but, although it does interesting things to renal function, it has failed to reduce blood pressure.<sup>87</sup> Goldblatt and his associates<sup>88</sup> have applied the same drugs to

\* J.A.M.A., 127:129, 1944.

animals with experimental hypertension and also found them valueless. There is no statistical proof that medical treatment reduces blood pressure or prolongs life.

**Paroxysmal Tachycardia**—Boyd and Scherf<sup>89</sup> revived interest in magnesium sulfate by reporting that the intravenous injection of 20 cc. of a 20 per cent solution terminated eight separate attacks.

### GASTROINTESTINAL TRACT

**Achlorhydria**—Koehler and Windsor<sup>90</sup> have reopened the problem of *acid therapy* in digestive diseases accompanied by achlorhydria. Titration experiments suggest that a normal meal evokes the secretion of about 35 cc. of dilute hydrochloric acid (U.S.P.) and that the normal pH of gastric contents after eating a meal containing 40 gm. of protein drops to about 1.6. To attain such a figure clinically would require the administration of 510 drops of dilute hydrochloric acid or 20 capsules of glutamic acid (420 mg. each) with each meal. This is a manifest impossibility and emphasizes the futility of the usual dosage.

**Peptic Ulcer**—Fogelson and Shoch<sup>91</sup> have suggested that the effectiveness of antacid therapy depends not on the neutralization of hydrochloric acid *per se* but on the consequent inactivation of pepsin. They claim to have produced symptomatic remission in twenty-six of thirty-four cases of intractable ulcer pain with *sodium alkyl sulfate*, a substance which inactivates pepsin without affecting the pH of gastric juice. *Sodium lauryl sulfate* (contained in Dreet) has received much publicity but we have seen no well controlled reports.

**Insoluble Sulfonamides**—Sulfaguanidine has proved to be too toxic. Succinylsulfathiazole and phthalylsulfathiazole (sulfasuxidine and sulfathalidine, Sharpe & Dohme, Inc.) have no effect on the typhoid-paratyphoid group of organisms or on protozoa, but they produce significant reduction in the total number of clostridia, anaerobic cocci and particularly of the coliform bacilli.<sup>92</sup> The antibacterial mechanism is unknown but the drugs are recovered from the stools in high concentration and little is reabsorbed into the blood stream.

**Bacillary dysentery** is well controlled by any sulfonamide. The acute phase is probably a systemic disorder and responds promptly to the soluble compounds, sulfathiazole and sulfadiazine being the most effective. For the chronic or carrier state, however, the insoluble preparations are to be preferred. Basing his opinion on the work of Hardy and associates,<sup>93</sup> Keefer<sup>94</sup> suggests that patients with acute dysentery be treated for four days with sulfadiazine and thereafter with sulfasuxidine until stool cultures are negative. Poth and Ross<sup>95</sup> later showed that sulfathalidine is much more effective than sulfasuxidine in the presence of watery diarrhea, the suggested scheme is 0.04 gm. for each kilogram of body weight every four hours for twelve doses, after which 0.02 gm. is given at four-hour intervals for at least seven days.

Flexner strains of *Shigella paradysenteriae* are more sensitive to sulfonamide action than the Sonne variety<sup>96</sup>

These authors, who treated six cases of *chronic ulcerative colitis* with 0.02 gm for each kilogram six times daily for four weeks, claimed satisfactory clinical response. Since the etiology of this disease is unknown, however, it can scarcely be regarded as curative. Our experience leads us to support Poth's<sup>92</sup> statement that "remissions can be initiated and sustained in approximately one-half of unselected cases of ulcerative colitis." Svartz<sup>97</sup> thought salicylazosulfapyridine the best drug for this disease. Doubtless others will be developed although the toxicity of sulfathalidine appears to be extremely low. If agranulocytosis appears, crude liver extract parenterally should be tried.<sup>98 154 155</sup>

Many surgeons feel that these compounds benefit the patient who is to undergo intestinal surgical procedures, some<sup>99</sup> even claiming that multiple stage operations for cancer of the colon are no longer necessary. It seems likely that these drugs might offer some protection against leaking through suture lines.

#### LIVER AND PANCREAS

**Experimental Hepatic Damage**—Studies of the effect on the liver of such toxic substances as phosphorus, carbon tetrachloride, arsenic, copper, alcohol, chloroform, selenium, manganese and tar have not been fruitful from the standpoint of human pathology. The experimental production, prevention and treatment of dietary hepatic injury, however, is a new and exciting field. Results are already so dramatic that it is probably no longer legitimate to advise such surgical procedures as splenectomy and omentopexy for patients with portal cirrhosis. For many years textbooks contained at least the implication that this disease is caused by an unidentified toxin but there is now enough evidence to justify the assumption that it is really a deficiency disorder. The prognosis is, of course, much brighter for those who receive an early diagnosis. Since similar experimental deficiencies have also produced profound degenerative changes in the kidneys and other organs,<sup>100</sup> it is to be hoped that more will be learned about such conditions as the "hepatorenal syndrome," bilateral cortical necrosis of the kidneys, nephrosis and other similar conditions.

György<sup>101</sup> has reviewed the experiences of himself and other investigators which have made it possible to produce regularly in rats the syndrome of fatty infiltration, necrosis and cirrhosis of the liver with jaundice, hypoproteinemia, ascites and pleural and pericardial effusion. He states that the hepatic lesions are strikingly similar to those of acute yellow atrophy in man and to those produced experimentally by such poisons as carbon tetrachloride. A diminished quantity of casein in the diet seems to be the important inciting factor. The administration of choline and cystine together or of methionine alone is effective in preventing and curing the disease. In transferring these results to man he calls attention to the fact that most alcoholics subsist on a low protein diet with an inadequate intake of the vitamin B complex (including choline). Anorexia, histologic changes in the liver and increased bromsulfalein retention<sup>102</sup> developed in dogs fed a vitamin B complex free diet. Chaikoff and Conner<sup>103</sup> believe that the presence of excessive amounts of fat in the liver lead slowly to fibrosis and cirrhosis. Ariel and his co-workers<sup>104</sup> review the evidence which supports the belief that a high concentration of lipids in the liver promotes ischemia and

dehydration and that adequate supplies of protein and glycogen protect the organ against various toxins Hough and his associates<sup>106</sup> have shown that in dogs fed a high fat diet deficient in protein or choline, there develop abnormal liver function tests which are improved by the ingestion of choline or methionine. The factors which predispose to liver damage seem to be, then, a low protein, high fat diet containing cystine but lacking in choline and other lipotropic factors listed below

**Lipotropic Substances**—Developments in this field are so new and so rapidly changing that no definite statements can be made Only the barest outline is presented here with the full realization that today's opinion will surely be modified tomorrow

Shortly after the discovery of insulin it was found that in depancreatized dogs maintained on insulin, there frequently developed fatty infiltration of the liver and that this change was preventable by feeding raw pancreas Lecithin was then found to be effective and when choline was identified by Best, Hershey and Huntsman<sup>106</sup> as the active constituent, the problem became alive Comprehensive reviews have recently appeared<sup>107 108</sup> Suffice it to say here that a large number of substances have been found which have lipotropic activity, i.e., they are able to prevent the deposition in and to accelerate the removal of fat from the liver under certain experimental conditions Conversely, there are other substances which increase the severity of nutritional hepatic damage The following is a partial list of these materials

#### *Lipotropes*

raw pancreas  
lecithin  
choline and derivatives  
betaine  
casein  
tyrosine  
methionine  
lipocaic  
cystine plus choline  
inositol  
ethanolamine

#### *Antilipotropes*

cystine  
cysteine  
homocysteine  
low protein, high fat diet  
cholesterol  
alcohol  
liver extract  
thiamine  
riboflavin  
pyridoxine  
pantothenic acid  
nicotinic acid  
biotin

There is much uncertainty about these lists and some of the contradictions may be more apparent than real The cystine effect may be nonspecific The presence of constituents of the vitamin B complex among the antilipotropes may represent nothing more than their capacity to assist in the conversion of carbohydrates into fats Lipocaic, claimed by Dragstedt and his co-workers<sup>109</sup> to be a new pancreatic hormone, may owe its activity to its content of choline, inositol and

other substances, in any event, there is no convincing evidence that it is really a hormone.<sup>110</sup>

The common denominator here is not apparent but it appears that choline is the important factor and that other substances may act as precursors of choline by contributing free or labile methyl radicals.<sup>111</sup> In ways which are not yet clearly understood choline is apparently concerned with the turnover of phospholipids.<sup>108</sup> It should be realized that not all fatty livers are alike, the effectiveness of a given lipotropic agent probably depends upon the chemical nature of the liver lipid in question. Obviously this field is in its clinical infancy.

*Clinical Implications*—In the management of hepatic disease György<sup>101</sup> suggests the employment of a high protein, low fat diet, supplemented by methionine (from 2 to 4 gm daily) or by cystine plus choline (from 2 to 4 gm of each daily). He thinks that these same measures should be employed when the liver has been damaged by burns, shock, anesthesia or poisons. Unfortunately, methionine, cystine and choline in these amounts are extremely expensive.

Miller and Whipple<sup>112</sup> have noticed that methionine or cystine plus choline are effective in combating the liver damage due to chloroform anesthesia. Goodell and associates<sup>113</sup> have shown that methionine protects dogs on a low protein diet from the hepatotoxic action of mapharsen. Beattie and his associates<sup>114</sup> successfully treated a case of carbon tetrachloride poisoning with infusions of a casein digest (amino acid) to which methionine was added. Ariel and his co-workers<sup>104</sup> suggest that "patients who frequently come to operation with fatty infiltration of their liver (as do those with gastro-intestinal cancer and bile duct obstruction) should be given preoperative glucose and lipocain in order to restore toward normal their altered hepatic chemical constitution." Patek and Post<sup>115</sup> made a major contribution to the therapy of Laennec's cirrhosis by showing the pronounced beneficial effects of a high protein, high carbohydrate, low fat diet supplemented by vitamin B complex concentrate. Fagin and Zinn<sup>116</sup> reported that the intravenous administration of amino acids in patients with cirrhosis of the liver is frequently followed by obvious clinical improvement. The importance of fatty infiltration of the liver in chronic alcoholism has been emphasized by Conner.<sup>117</sup> One may expect to see reports dealing with the dietary treatment of the fatty livers seen also in diabetes mellitus, hypothyroidism, Wilson's disease and epidemic hepatitis. Such studies are urgently needed in the latter disorder particularly.

*Pancreatic Insufficiency*—Textbooks of pharmacology generally give the impression that oral administration of pancreatic enzyme is ineffective. Recent clinical experiences, however, point to their efficacy in the management of pancreatic steatorrhea.<sup>118, 119, 120</sup> Triple strength pancreatin in enteric-coated capsules is available but must be given in daily doses of 12 to 25 gm.

## BLOOD AND BLOOD SUBSTITUTES

**Blood Coagulation**—The problem of the relationship of *aspirin* to epistaxis and gastric hemorrhage has been brought forward again by some very interesting findings Paul<sup>121</sup> performed gastroscopic examinations in 182 patients, 107 had no abnormalities, sixty-two had chronic gastritis and thirteen showed evidence of ulceration, polyps or carcinoma After the administration of 15 grains of aspirin, no evidence of hemorrhage, hyperemia or other physical changes in the gastric mucosa was observed Thirty-nine other cases of ulcer or dyspepsia were observed twenty-four hours after the ingestion of 50 to 80 grains of aspirin and no tendency to hemorrhage was noted Seven other patients who had a history of hemorrhage following the use of aspirin were examined following the ingestion of aspirin with negative findings

At about this time, Link and his associates<sup>122</sup> showed that dicoumarol was broken down in the body into salicylic acid and that salicylates in rats produced prothrombinopenia which could be prevented by the administration of *vitamin K* These discoveries have been applied to humans by several observers<sup>123 124</sup> They have shown that the administration of salicylates increases the prothrombin time, especially if salicylate therapy is prolonged It has been calculated<sup>125</sup> that 1 mg of vitamin K will approximately counteract the action of 1 gm of salicylic acid on the prothrombin time

It is to be noted that the average dose of vitamin K in the form of menadione bisulfite is 1 to 5 mg daily Dicoumarol has been found to exert its action by inhibiting the formation of prothrombin and causing a prothrombinopenia The usual therapeutic doses of vitamin K do not prevent this action Large amounts of synthetic vitamin K such as 64 mg in single doses, have produced satisfactory responses in all but two with prothrombinopenia induced by dicoumarol<sup>126</sup> These large amounts of vitamin K caused no toxic reactions

The problem of the use of *dicoumarol* is far from settled<sup>127</sup> Dicoumarol has the advantage of being extremely inexpensive, it can be given by mouth and by lowering the prothrombin time might be expected to prevent thrombosis It does not delay coagulation and may cause serious bleeding As previously noted, however, if spontaneous hemorrhage occurs, synthetic vitamin K may be used or the natural vitamin K<sub>1</sub> oxide<sup>127a</sup> or blood or plasma given In comparison with heparin, the action of dicoumarol is relatively slow in development and disappearance It is clear that patients receiving dicoumarol should have frequent determinations of the prothrombin time Quick<sup>128</sup> has produced evidence suggesting that prothrombin may have two components One part (A) decreases on cold storage, the other (B) is affected by dicoumarol and vitamin K deficiency Banked plasma which loses component A, is however effective for treatment of prothrombinopenia due to dicoumarol

A comparison of dicoumarol and heparin is given in the accompanying table

	<i>Dicoumarol</i>	<i>Heparin</i>
Mechanism of action	Prevents prothrombin formation*	Blocks action of prothrombin† or thrombin
Rapidity of action	In 24-48 hours	Immediate
Duration of action	Prolonged	Transitory
Method of control	Prothrombin time	Clotting time
Toxic effects	Predisposes to hemorrhage	Predisposes to hemorrhage
Method of administration	Oral	Intravenous or intramuscular in beeswax
Cost	Cheap	Relatively expensive

*Heparin* seems to be of considerable value in the treatment of venous thrombosis and pulmonary embolism, and as is well known, its effect is to prolong the coagulation time of the blood. Consequently, if heparin is used, the coagulation time must be observed daily. De Takats<sup>120</sup> has developed a test for heparin tolerance in which the patient's coagulation time after a standard intravenous dose of heparin is determined. This test indicates that some patients are resistant to heparin, and vice versa. He, as well as Rhoads and his associates<sup>130</sup> and others,<sup>137</sup> believe the dicoumarol and heparin should be used together.

Thus, a single intravenous dose of 5 cc of heparin can be given immediately in a case of emergency, followed by intramuscular doses. Bryson and Code<sup>131</sup> have administered a suspension of powdered heparin and beeswax subcutaneously and have found that a prolonged coagulation time will develop in the experimental animal. Following the intravenous administration of heparin, dicoumarol may be begun by mouth. In a series of fifteen patients reported by Rhoads, Walker and Panzer<sup>130</sup> there have been no accidents, but in one year we saw three cases of cerebral hemorrhage occur during heparinization. It is suggested that the prothrombin time be maintained somewhere between thirty-five and sixty seconds while dicoumarol is being used. Caution should be taken in the administration of the drug in those cases with ulcerating or granulating wounds or liver disease, and it is now believed to be contraindicated in subacute bacterial endocarditis.<sup>132</sup> We suspect that the use of these materials will soon become unfashionable.

Of related interest is the report by de Takats, Trump and Gilbert<sup>133</sup> on the effects of *digitalis* on the blood-clotting mechanism. Their studies suggest that *digitalis* favors a tendency toward thrombosis which becomes particularly pronounced in patients with stasis or infection. They have suggested the use of sodium tetrathionate as a drug

Through an inability of the liver to utilize vitamin K

† By union of its mucotin-sulfuric acid like property with an unidentified serum albumin factor. The compound thus formed appears to bind thrombin<sup>133a</sup> or prevent the invasion of prothrombin to thrombin<sup>133b</sup>



to oppose the thrombotic tendency of digitalis This drug is administered intravenously

**Red Blood Cells**—The war has served to accelerate studies on the use of blood and blood substitutes for shock and various other conditions One of these new developments is in regard to the control of hemorrhage associated with severe damage to the liver Kinsey,<sup>184</sup> in five cases of acute yellow atrophy of the liver with hemorrhagic tendency, gave blood transfusions, the blood being fortified by the administration of vitamin K to the donor In four of these cases the method seemed to have a remarkable effect in controlling the bleeding tendencies

For the most part in the present war emergency, blood plasma has been extensively used and is apparently of much greater value in the treatment of shock and burns than whole blood This extensive use of plasma alone has made available large quantities of red blood cells which are usually discarded Murray, Hale and Shaar<sup>185</sup> and Taylor and associates<sup>186</sup> describe a method of preparing a *suspension of discarded red blood cells* in 5 per cent dextrose and/or isotonic solution of sodium chloride In a period of ten weeks Murray gave more than 116 infusions of this red blood cell suspension to patients with anemia The rationale for the use of the red blood cells was that in anemia the only substance needing restoration was the red blood cells themselves They noted two reactions, an incidence of 17 per cent The average rise of hemoglobin for each 300 cc of suspension was approximately 1 gm and all but four of the cases showed clinical improvement Taylor reports on 18,000 such transfusions Another observer has reported the use of a paste of red blood cells in the treatment of chronic ulcerated conditions of the extremities

**Fibrin**—Two problems awaiting solution in neurosurgery are those connected with hemostasis and those related to the prevention of meningocerebral adhesions An article by Ingraham and Bailey<sup>187</sup> describes the experimental, clinical and pathologic studies on the use of *fibrin foam* as a hemostatic agent and of fibrin film as a substitute for the dura to prevent meningocerebral adhesions Fibrin foam is prepared from human fibrinogen and human thrombin At operation thrombin is dissolved in a saline solution and then the fibrin foam is placed in the thrombin solution and pieces of various sizes and shapes can be selected for use in different conditions The use of the material has shortened neurosurgical operations because of better hemostasis, especially the oozing of blood from the beds of tumors The fibrin foam has also been used with agents such as sulfadiazine and penicillin which apparently do not change the properties of the foam or the tissue reaction

Previous studies of the problem of cerebral adhesions have shown that the ingrowth of dural substitutes into the cerebral wound is the most important factor in postoperative convulsions Ingraham and

Bailey used *fibrin film* composed of 1 part protein and 1 part a plasticizing agent. The protein part is approximately 90 per cent fibrin. The films are smooth, occurring in sheets, and are somewhat elastic. They may be sutured without tearing and can be easily cut to fit any dural defect. Thus far, observations have been made in patients who have had this fibrin film left over the cerebral cortex for a period of eight months and no evidence of cortical irritation has been noted. As with fibrin film, sulfadiazine and penicillin may be used without apparent ill effects on the fibrin film.

**Bovine Plasma.**—Much effort is being directed toward the problem of preparing animal plasma for use in humans. A recent report by Edwards<sup>138</sup> is promising in that he has reported no serious toxic reactions in twenty-six patients to whom he gave large amounts of a specially treated bovine serum.

**Human Albumin.**—Fractionation of plasma by Cohn and his associates<sup>139</sup> has provided a concentrated blood derivative (albumin) for emergency use. Each gram of albumin is equivalent to 12 gm of plasma protein or 20 cc. of Red Cross citrated pooled plasma. The standard Army and Navy package contains 25 cc. of albumin in 100 cc of a diluent. Its osmotic effect is equivalent to 500 cc. of citrated plasma.<sup>140</sup> It is effective in shock due to trauma, hemorrhage, operations or burns. In patients with chronic hypoproteinemia due to liver cirrhosis or nephrosis the beneficial effects were temporary.<sup>141, 142, 143</sup>

**Miscellaneous.**—Gelatin solutions have been suggested as a substitute for plasma. As indicated by a report of the National Research Council,<sup>144</sup> there are definite limitations and many unanswered questions concerning its use. Gelatin is not yet considered a satisfactory substitute for albumin or plasma.

**Amino Acids.**—Elman,<sup>145</sup> who has done so much to advance the cause of parenteral alimentation, has recently reviewed this problem. He points out that whereas a completely satisfactory diet cannot be yet given intravenously, largely because of difficulties concerned with the preparation of fats, it is now possible to give in one liter of solution all of the known protein, carbohydrate, vitamin and mineral constituents. The protein equivalent of 4 units of plasma can be given in the form of 50 gm of casein digest (Amigen, Mead Johnson & Co.), this contains all of the essential amino acids, will keep the average patient in nitrogen balance, and to it may be added required amounts of sugar, salt and synthetic vitamins. Hartmann, Lawler and Mecker<sup>146</sup> have reported the successful use of these principles in infant nutrition.

#### ENDOCRINE SYSTEM

**Thyrotoxicosis.**—Astwood<sup>147</sup> revolutionized the treatment of thyrotoxicosis by the introduction of thiourea and related compounds. A complete review of the physiologic principals involved is not possible here, but they are covered by Rawson and his group<sup>148</sup> who state that

*thiouracil* induces symptomatic remission in exophthalmic goiter by interfering with the synthesis of thyroid hormone within the thyroid gland. Continued administration produces myxedema and pronounced hyperplasia of the thyroid, the latter because of increased production of the thyrotropic hormone by the anterior pituitary. Williams and Clute<sup>149</sup> have reported their clinical experiences with seventy-two cases of thyrotoxicosis, in all of whom thiouracil caused lowering of the basal metabolic rate, return to normal of the protein-bound iodine of the plasma and satisfactory clinical remission. Himsworth<sup>150</sup> has also had satisfactory results in thirty-two cases but describes a number of untoward reactions. It is too early to state that subtotal thyroidectomy for exophthalmic goiter has been made obsolete by this extremely important drug, but we have not yet found operation necessary since the drug became available to us. In a much smaller experience we have had entirely satisfactory results and only one mild skin eruption as a toxic manifestation. The daily ingestion of 0.6 gm of thiouracil produces a dramatic remission in approximately three weeks, after which a maintenance dose of 0.1 or 0.2 gm daily is given for about six months to prevent recurrence. Its mechanism of action is entirely different from that of iodine, but it is also more satisfactory than Lugol's solution in preparation of the patient for thyroidectomy, should that be thought necessary. Occasionally, exophthalmos may be accentuated, as sometimes occurs after operation, but Salter and Soley<sup>151</sup> have described the successful use of large amounts of desiccated thyroid in the treatment of malignant exophthalmos, on the theory that thyroid suppresses the manufacture of thyrotropic hormones.

The most serious reactions from thiouracil have been due to agranulocytosis.<sup>152</sup> Parenteral liver extracts and folic acid have been suggested as specific remedies.<sup>153</sup> Others<sup>154, 155</sup> had previously shown that these materials were effective antidotes for leukopenias produced by sulfaguanidine.

**Myxedema**—Proloid (Maltine Co.) is said to possess the calorogenic activity of desiccated thyroid without the sometimes troublesome cardio-accelerating properties.

**Parathyroid Tetany**—Until recently parathyroid tetany has been treated by parathormone or A.T. 10. Recent work by several investigators<sup>156-160</sup> has indicated that *massive doses of vitamin D*, up to 200,000 U.S.P. units a day, with added calcium by mouth will prevent parathyroid tetany. They have found no evidence of toxicity, such as hypercalcemia or renal disturbances. This type of therapy is economically cheaper than previous methods. Pope and Aub<sup>161</sup> have summarized the recent literature on the parathyroid glands. It is believed that vitamin D influences mainly the absorption of calcium from the gastrointestinal tract, that the parathyroid hormone acts only on phosphorus excretion by the kidneys, and A.T. 10 is effective in promoting the excretion of urinary phosphorus and in large amounts will also

aid calcium absorption. Studies by Albright and associates<sup>102</sup> have suggested that *aluminum hydroxide* be used in the treatment of hypoparathyroidism, as this drug tends to combine with the phosphorus in the intestinal tract, aiding its excretion thereby, as a consequence the serum phosphorus is lowered and the serum calcium is elevated. It has also been suggested by Thorn<sup>103</sup> that aluminum hydroxide be used in chronic nephritis with tetany on the same rationale.

**Addison's Disease**—No important therapeutic advances since the introduction of pellet implantation in Addison's disease have been reported. Selye, Hall and Rowley<sup>104</sup> reported the occurrence of vascular lesions in rats, dogs and other animals after prolonged administration of *desoxycorticosterone acetate* and sodium chloride. Perera and associates<sup>105</sup> noted the development of hypertension in eight of twenty-four patients with Addison's disease treated with desoxycorticosterone acetate. As in animals, this rise did not occur on salt alone. They then gave the drug *without salt* to three normal persons and observed a gradual rise of blood pressure which returned to normal within two weeks after the drug was withdrawn. There was neither abnormal retention of the sodium ion nor any increase in the circulating blood volume. The effect apparently was not due to an abnormally labile vascular system as measured by the cold pressor test.

**Estrogenic Therapy**—Recent investigations have suggested the exciting possibility of using estrogens in the therapy of *prostatic cancer*. Huggins<sup>106</sup> believes that estrogens counteract the stimulating effect of androgens on the tumor cells. In prostatic cancer, especially with metastases, it has been known for some time that the serum acid phosphatase is increased. Several investigators<sup>107-109</sup> have found that the use of estrogens, with or without orchiectomy, has reduced serum phosphatase; this suggests a decrease in the activity of the tumor cells. The results indicate that life is prolonged, the patient is made much more comfortable and metastases may even disappear by means of this treatment. As might be expected, it is by no means a perfect treatment, one distressing complication being pain and swelling of the male breasts.

Enthusiastic reports of a number of new estrogenic substances have appeared. These are mostly synthetic products to be taken orally and the prime reason for their appearance seems to be the claim for greater potency with decreased toxicity, such as nausea and bleeding. Among these new estrogenic substances are (1) ethinyl estradiol (Schering Corp.)<sup>170</sup> 15 micrograms daily in enteric coated tablets for twenty-one days followed by withdrawal for one week, (2) octofollin (Schueffelin & Co.)<sup>171-174</sup> in doses of 2 to 10 mg by mouth for from four to seven days (it can also be used in oil for deep intramuscular injections),<sup>171</sup> and (3) dienestrol (hextestrol, Wm S Merrill Co.) in doses of from 1 to 4 mg.<sup>175, 176</sup>

Articles by McCullagh<sup>177</sup> and Smith<sup>178</sup> give excellent reviews of the

use of female sex hormones in such functional disorders as amenorrhea, dysmenorrhea, uterine bleeding, menopause, sterility, premenstrual tension and headaches. Estrogens are also apparently extremely effective in the suppression of lactation. In addition to estrogens in the treatment of premenstrual edema, tension and headaches, McCullagh<sup>177</sup> has re-emphasized limitation of salt intake and suggested the use of ammonium chloride in the second half of the menstrual cycle.

**Androgenic Therapy**—Using the same rationale for the use of estrogens in the treatment of prostatic cancer, various authors<sup>179-183</sup> have been investigating the effects of testosterone propionate in the treatment of cancer of the breast. Insufficient time of observation, as well as lack of an adequate number of patients studied, does not permit one to state how effective this therapy might be, aside from the reduction of pain in at least 50 per cent of the cases thus far treated.

It is not the purpose here to discuss the use of testosterone propionate in the treatment of angina pectoris, various endocrine abnormalities or cryptorchidism. It has been found, however, that testosterone propionate will cause retention of nitrogen and revert a patient with a negative nitrogen balance into one with a positive balance.<sup>184-190</sup> Because of this action, Bassett and associates<sup>191</sup> have tried testosterone in the treatment of nephrosis, a condition in which there is a constant loss of protein with reduction of the plasma protein level. Their protocol of a 24 year old nephrotic man shows conversion to body protein of 41 per cent of the ingested protein when testosterone propionate was used in comparison to other regimens. About one half of the extra nitrogen utilized contributed to increased proteinuria and the rest was retained in the body. This increase of proteinuria with the slight rise of the concentration of serum protein suggests that there was some increase in the synthesis of plasma protein. They noted, however, that the administration of the drug was associated with the retention of salt and water and the accentuation of edema.

**Islets of Langerhans**—One of the most fascinating developments regarding diabetes mellitus has been its experimental production in rabbits and rats by the injection of *alloxan*. Observers<sup>192-196</sup> have shown that this drug causes necrosis of the pancreatic islet tissue and this is followed by persistent glycosuria and hyperglycemia. Further resemblance to the disease in human beings was provided by Bailey, Bailey and Leech,<sup>197</sup> who from four to six weeks after the induction of diabetes in rabbits, found cataracts, slight fatty changes in the liver and some mild tubular degeneration of the kidneys. Because of this specific necrotizing action of alloxan on the beta cells of the pancreas, Brunschwig<sup>198, 199</sup> injected alloxan into a patient with carcinoma of the pancreas with liver metastases who had recurring attacks of hyperinsulinism of increasing frequency and severity. He believed that this produced significant decrease in the number of attacks. The patient died following laparotomy but the postmortem examination did not reveal necrosis in the malignant islet cells of the liver or elsewhere.

In the treatment of diabetes mellitus a new type of insulin has been placed on the market. It is termed *globin insulin* (Burroughs Wellcome

& Co.), containing 80 units of insulin for each cubic centimeter<sup>200-203</sup> The onset of the duration of its action is between that of regular insulin and protaminc zinc insulin Its hyperglycemic effect may be found two hours after subcutaneous injection and increases rapidly thereafter with a maximum effect coming between the eighth and sixteenth hour after injection The effect gradually wears off thereafter and is practically absent at the end of twenty-four hours The main advantage seems to be the lack of overlapping action with the dose given the next day Furthermore, its maximum activity, if given before breakfast, is associated with the largest meal of the day and during the night the action gradually wears off Bedtime feedings are therefore seldom necessary However, it may precipitate attacks of hyperglycemia, usually late in the afternoon so that supplemental feedings may be necessary

### LUNG

One of the most significant possibilities in therapeutics was reported in the article by Crombie and his associates<sup>204</sup> on the *treatment of silicosis* by an *aluminum powder* At the present time it is believed that silica changes to silicic acid in the tissues which are destroyed, with resulting fibrosis In 1936 it had been discovered by Denny and Robinson<sup>205</sup> that aluminum powder prevented the solution of silicates, the mechanism for which was subsequently found to be due to the coating of the silica particles by a film of crystalline alpha aluminum monohydrate boehmite. In animal experiments it was found that the addition of 1 per cent aluminum powder to inhaled silica dust prevented the occurrence of silicosis, even after prolonged exposure up to twenty-two months

After a careful examination, thirty-four patients with silicosis were treated. Eighteen of these showed little or no disability Eight had complicated conditions, three of whom showed a definitely measurable disability Treatment consisted of the inhalation of aluminum powder through a special apparatus in gradually increasing doses of periods of exposure up to thirty minutes daily for six days a week until two hundred to three hundred treatments had been administered. The following results of the treatment were reported 19 or 55 per cent showed diminution or disappearance of dyspnea, cough, pain in the chest and fatigue. No changes were observed in fifteen cases. Tests of respiratory function showed improvement in twelve of the thirty-six patients Of a group of nine controls who were not treated by aluminum, evidence of progression of the disease was observed in six

### MISCELLANEOUS

**Lead Poisoning.**—Kety and Letonoff<sup>206</sup> advocate the administration of *sodium citrate* for the treatment of acute and chronic lead poisoning on the grounds that lead citrate is more soluble and diffusible. The

probable mode of excretion is through the liver, in any event they found that a pronounced decrease in the concentration of blood lead was quickly produced and that satisfactory clinical remission soon followed. In severe cases, 50 cc of a 2.5 per cent solution of sodium citrate was given intravenously. In more chronic cases the drug is administered orally in doses of from 4 to 5 gm in a little water three or four times daily.

**Histamine Desensitization**—The use of *histamine-azoproteum* (haphamine, Parke Davis & Co) in the treatment of allergic disorders has been discussed elsewhere in this symposium (Derbes). We have no rational justification for its use in migraine but have been astonished by the number of patients with periodic headache who claim to have experienced pronounced relief from its use. It is given subcutaneously in ascending doses at intervals of from five to seven days, the average maintenance dose being 0.25 cc. The manufacturers claim that it is a more effective antibody-producer than is plain histamine itself.<sup>208a</sup>

**Chemotherapy of Shock**—In an extraordinary paper, Fox<sup>207</sup> has reported the successful treatment of severely burned and shocked patients with orally administered *sodium lactate* instead of plasma infusions. By using radioactive sodium he has demonstrated that traumatized skin contains enormous quantities of base and feels that this is at least partially responsible for the great reduction in plasma volume. Basing his clinical studies on the experimental work of Rosenthal,<sup>208 209</sup> Fox administered from 7 to 10 liters of one-sixth molar sodium lactate by mouth within the first twenty-four hours and claimed a rapid increase in blood volume without alkalosis. This paper needs careful confirmation, as in many respects it runs counter to accepted ideas regarding shock. It has been skeptically discussed by Harkins<sup>210</sup> and Cope.<sup>211</sup>

**Syphilis**—*Dichlorophenarsine hydrochloride* has been accepted officially as a safe arsenical for the treatment of syphilis and related conditions. It is more stable, apparently less toxic and possesses a less disagreeable taste than *oxophenarsine hydrochloride* (mapharsen).

**Fungus Infections**—*Sodium propionate* for the local treatment of fungus infections was introduced by Keeney<sup>212</sup> with encouraging preliminary results. At a pH of 5.5 in a 1.24 per cent solution of sodium propionate it was found to be fungistatic. Its optimal fungicidal activity, however, existed only in solutions of from 10 to 20 per cent.

#### BIBLIOGRAPHY

1. Eisleb, O. and Schaumann, O. *Deutsche med. Wchnschr.*, 65:967-968 (June 16) 1939.
2. Schaumann, O. *Arch. f. exper. Path. u. Pharmacol.*, 196:109-136, 1940.
3. Duguid, A. M. E. and Heathcote, R. St. A. *Quart. J. Pharm. & Pharmacol.*, 13:318-331 (Oct.-Dec.) 1940.
4. Gruber, C. M., Haury, V. G. and Drake, M. E. *Arch. Internat. de pharmacodyn. et de therap.*, 64:308-312 (April 30) 1940.

- 5 Clumenko D R., *Feder Proc.*, 1 15 (March) 1942
- 6 Yonkman, F F., Noth P H and Hecht, H H., *Ann Int. Med.*, 21 7-16 (July) 1944
- 7 Hoffman, R., *Anesth & Anal.*, 22 336-340 (Nov.-Dec.) 1943
- 8 Noth, P H., Hecht, H H and Yonkman F E., *Ann Int. Med.*, 21 17-34 (July) 1944
- 9 Batterman, R. C., *Arch Int. Med.*, 71 345-356 (March) 1943
- 10 Batterman, R. C. and Himmelsbach C. K., *J.A.M.A.*, 122 222-226 (May 22) 1943
- 11 Batterman, R. C., *Connecticut M J.*, 8 13-17 (Jan.) 1944
- 12 Hecht, H., Noth P H. and Yonkman F F., *J.A.M.A.*, 121 1307 (April 17) 1943
- 13 Rovenstone, E. A. and Batterman R. C., *Anesthesiology*, 4 126-134 (March) 1943
- 14 Batterman, R. C. and Mulholland J H., *Arch Surg.*, 46 404-409 (March) 1943
- 15 Gilbert G and Dixon, A B., *Am. J. Obst. & Gynec.*, 45 320-326 (Feb.) 1943
- 16 Roby C. and Schaumann, W R., *Am J Obst. & Gynec.*, 45 318-319 (Feb.) 1943
- 17 White, C. S. M., *Ann District of Columbia*, 12 388-390 (Oct.) 1943
- 18 Barlow O W., Quoted by Batterman, R. C. and Himmelsbach C. K., 10
- 19 Himmelsbach, C. K., *J Pharmacol. & Exper Therap.*, 75 64-68 (May) 1942
- 20 Andrews, H L., *J Pharmacol. & Exper Therap.*, 76 89-94 (Sept.) 1942
- 21 Andrews, H L., *J Pharmacol. & Exper Therap.*, 79 5-9 (Sept.) 1943
- 22 Himmelsbach, C. K., *J Pharmacol. & Exper Therap.*, 73 322-328 (April) 1944
- 23 Jones, C. M. and Chapman W P., *Arch. Int. Med.*, 4 101 1943
- 24 Roy Nav Med Bull No 2 15-16, 1943 in Bull. War Med., 4 101 1943
- 25 Anderson, E. W., *J Roy Nav Med. Serv.*, 28 361-377 (Oct.) 1942 in Bull War Med., 4 582 1943
- 26 Beaton, L. E. et al., *Arch. Neurol & Psychiat.*, 49 518-536 (April) 1943
- 27 Bathurst, Norman H., *J Roy Army M. Corps*, 81 145-147 (Sept.) 1943
- 28 Hazleton, L. W., *J Am. Pharm. Assn. (Sc. ed.)*, 33 65-73 (March) 1944
- 29 Soskin, S. and Taobenhaus, M., *J Pharmacol. & Exper Therap.*, 78 49-55 (May) 1943
- 30 Holling H E., McArdle, B. and Trotter W R., *Lancet*, 1 127-129 (Jan. 22) 1944
- 31 Waelch, H. and Price, J. C., *Arch Neurol & Psychiat.*, 51 393-396 (April) 1944
- 32 Nicholson, M. J., *New England J Med.*, 229 244-250 (Aug 5) 1943
- 3 DeWaal H L., Kanaar A. C. and McNaughton J., *Lancet*, 2 724-727 (Dec 19) 1942
- 4 Gaysunsky B E., *Klirurgiya No 6*, 13-15 1939
- 35 Ochsmier A., *S. Clin North America*, 23 1318-1334 (Oct.) 1943
- 36 Gorrell, R. L., *Am. J. Surg.*, 63 102-104 (Jan.) 1944
- 37 Findley T. and Patzer R., To be published
- 38 Gius, J. A., *Surgery*, 8 832-838 (Nov.) 1940
- 39 Starr A. and Gilman, S., 227 102-104 (July 16) 1942
- 40 Lee, F. C., Macht, D. I. and Pierpont, R. Z., *Bull. Johns Hopkins Hosp.*, 74 119-120 (Feb.) 1944
- 41 Kittredge, W. E. and Brown, H. G., *New Orleans M & S J*, 96 562-567 (June) 1944
- 42 Altschule, M. D. and Iglauer A., *J Clin. Investigation*, 19 497-502 (May) 1940.
- 43 Iglauer A. and Altschule, M. D., *J Clin. Investigation*, 19 503-514 (May) 1940.



- 44 Stead, E A., Jr and Kunkel, P J Clin Investigation, 18 439-448 (July) 1939
- 45 Kunkel, P., Stead, E. A., Jr and Weiss, S J Clin. Investigation, 18 679-685 (Nov) 1939
- 46 Ranges, H A. and Bradley, S E. J Clin Investigation, 22 687-693 (Sept.) 1943.
- 47 Ivy, A. C and Goetzel, F R War Med, 3 60-77 (Jan) 1943
- 48 Eaton, L M Proc Staff Meet., Mayo Clin., 18 262-264 (July 28) 1943
- 49 Beaser, S H, Lipton, J H and Altschule, M D Am J M Sc., 206 490-497 (Oct) 1943
- 50 Guttman, S A. Arch Neurol & Psychiat., 51 568-569 (June) 1944
- 51 Wilson, A and Stoner, H B Quart J Med., 13 1-18 (Jan) 1944
- 52 Torda, Clara and Wolff, H G Science, 98 224-225 (Sept. 3) 1943
- 53 Viets, H R Lancet, 1 33-34 (Jan. 1) 1944
- 54 Wilson, A. and Stoner, H B Lancet, 1 429-431 (April 1) 1944
- 55 Bennett, A E. and Cash, P T Dis Nerv System, 4 299-301 (Oct.) 1943
- 56 Harvey, A M J.A.M.A., 112 1562-1563 (April 22) 1939
- 57 Minot, A. S., Dodd, K. and Riven, S S J.A.M.A., 113 553 (Aug 12) 1939
- 58 Dynes, J B J Nerv & Ment. Dis., 98 48-55 (July) 1943
- 59 Gammon, G D, Harvey, A M and Masland, R. L Biol. Symposia, 3 291-330, 1941
- 60 Wolf, A New York State J Med., 43.1951-1963 (Oct. 15) 1943
- 61 Forster, F M and Alpers, B J Arch Neurol & Psychiat., 51 264-267 (March) 1944
- 62 Kabat, H and Knapp, M E J Pediat., 24.123-137 (Feb) 1944
- 63 Trommer, P R and Cohen, A J.A.M.A., 124 1237-1239 (April 29) 1944
- 64 Cullen, S C Surgery, 14 261-266 (Aug) 1943
- 65 Baird, J W and Adams, R C Proc Staff Meet., Mayo Clin, 19 200-201 (April 19) 1944
- 66 Bennett, A. E J.A.M.A., 114 322-324 (Jan 27) 1940
- 67 Gold, H et al J.A.M.A., 119 928-932 (July 18) 1942
- 68 Fahr, G and LaDue, J Am Heart J., 21 133-150 (Feb) 1941
- 69 Chamberlain, F L and Sokolow, M Am Heart J, 23 245-246 (Feb) 1942
- 70 Parsonnet, A. E. and Bernstein, A Am Heart J, 26 39-41 (July) 1943
- 71 Nicholson, J H New England J Med., 229 619-621 (Oct. 14) 1943
- 72 Schwab, E H Texas State J Med., 35 619-622 (Jan) 1940
- 73 Eichna, L W and Taube, H Am Heart J., 26 631-644 (Nov) 1943
- 74 Eichna, L W and Taube, H Am Heart J., 27 641-656 (May) 1944
- 75 Chen, K K et al J Pharmacol & Exper Therap, 77 401-406 (April) 1943
- 76 Batterman, R C, DeGraff, A. C and Rose, O A. Am Heart J., 21 98-103 (Jan) 1941
- 77 Batterman, R C., DeGraff, A. C and McCormack, J E. J.A.M.A., 124 1243-1247 (April 29) 1944
- 78 Wexler, Jack and Ellis, L B Am Heart J, 27 86-95 (Jan) 1944
- 79 Coburn, A. F Bull Johns Hopkins Hosp., 73 435-464 (Dec) 1943
- 80 Smull, Katharine, Wegria, Rene and Leland, Jessica J.A.M.A., 125 1173-1175 (Aug 26) 1944
- 81 Holbrook, W P J.A.M.A., 126 84-87 (Sept. 9) 1944
- 81a. Coburn, A. F J.A.M.A., 126 88-93 (Sept. 9) 1944
- 82 Levine, S A New England J Med, 229 770-772 (Nov 18) 1943
- 83 Mosenthal, H O J.A.M.A., 114 1548-1552 (April 20) 1940
- 84 Evans, W E and Loughnan, O Brit. Heart J, 1 199-228, 1939
- 85 Kapernick, J S Am Heart J, 26 610-622 (Nov) 1943
- 86 Goldring, W and Chasis, T T Commonwealth Fund, 1944
- 87 Taylor, R. D et al Am J M Sc., 206 659-667 (Nov) 1943

88. Goldblatt, H., Kahn, J. R. and Lewis, H. A. J.A.M.A., 119 1192-1201 (Aug 8) 1942
89. Boyd L. J and Scherf, D. Am J M Sc., 206 43-48 (July) 1943
90. Koehler A. E. and Windsor E. Ann. Int. Med., 18 182-192 (Feb) 1943
91. Fogelson, S. J. and Shoch, D. E. Arch. Int. Med., 73 212-216 (March) 1944
92. Poth E. J. Internat. Abst Surg., 78 373-380 (May) 1944 in Surg., Gynec & Obst. (May) 1944
93. Hardy A. V., Burns, W. and DeCapito T.. Pub Health Rep., 58 689-693 (April 30) 1943
94. Keefer C. S. M. Clin. North America, 27 1201-1211 (Sept.) 1943
95. Poth, E. J. and Ross, C. A. J. Lab & Clin Med., 29 785-808 (Aug) 1944
96. Hardy A. V. and Watts J. J.A.M.A., 124 1173-1178 (April 22) 1944
97. Svartz, N. Gastro-enterologia, 66 312-322 1942
98. Spicer S. S. et al. Pub Health Rep., 57 1559-1566 (Oct. 16) 1942
99. Archer H. L. and Lehman, E. P. Ann. Surg., 119 518-525 (April) 1944
100. Griffith, W. H. Biol. Symposia 5 193-212 1941
101. Gyorgy P. Am. J. Clin. Path., 14 67-88 (Feb) 1944
102. Drill, V. A., Shaffer C. B. and Leatham, J. H. Proc. Soc. Exper Biol & Med., 52 328-330 (April) 1943
103. Chaikoff I. L. and Conner C. L.. Proc. Soc. Exper Biol & Med. 43 638-641 (April) 1940
104. Arel, I. M. et al.. Ann. Int. Med., 20 570-589 (April) 1944
105. Hough V. H. et al. Am J Physiol., 139 642-651 (Aug) 1943
106. Best, C. H., Hershey J. M. and Huntsman, Elmer J. Physiol., 75 56-66 (May 30) 1932
107. Best, C. H. and Lucas, C. C. Vitamins and Hormones edited by R. S. Harris and K. V. Themann 11 1943
108. McHenry E. W. and Patterson, Jean. Physiol. Rev., 24 128-167 (Jan.) 1944
109. Dragstedt L. R., Van Prohaska, J. and Harris H. P. Am J Physiol., 117 175-181 (Sept.) 1936
110. Entenman, C., Montgomery M. L. and Chaikoff I. L. Am. J. Physiol., 141 221-226 (April) 1944
111. duVigneaud, V. et al. J. Biol. Chem., 131 57-76 (Nov) 1939
112. Miller L. L. and Whipple, G. H. J. Exper. Med., 76 421-435 (Nov) 1942
113. Goodell, J. P. B., Hanson, P. C. and Hawkins, W. B. J. Exper. Med., 79 625-632 (June 1) 1944
114. Beattie, J. et al. Brit. M. J., 1 209-211 (Feb 12) 1944
115. Patek, A. J., Jr. and Post, J. J. Clin. Investigation, 20 481-505 (Sept.) 1941
116. Fagin, L. D. and Zinn F. T.. J. Lab & Clin. Med., 27 1400-1409 (Aug) 1941
117. Conner C. L. J.A.M.A., 112 387-390 (Feb 4) 1939
118. Beazell, J. M., Schmidt, C. R. and Iry, A. C. J.A.M.A., 116 2735-2739 (June 21) 1941
119. Lake, M., Cornell, N. W. and Harrison, H. E. Am J M. Sc., 205 118-122 (Jan) 1943
120. Farber S., Shwachman, H. and Maddock, Charlotte J. Clin. Investigation, 22 827-838 (Nov) 1943
121. Paul W. D.. J. Iowa M. Soc., 33 155-158 (April) 1943
122. Link, K. P. et al. J. Biol. Chem., 147 463-474 (Feb) 1943
123. Meyer O. O. and Howard, B. Proc. Soc. Exper Biol & Med., 53 234-237 (June) 1943
124. Shapiro S.. Proc. Soc. Exper Biol & Med., 53 251-254 (June) 1943
125. Shapiro S. J.A.M.A., 125 546-548 (June 24) 1944
126. Cromer H. E., Jr. and Barker N. W.. Proc. Staff Allect., Mayo Clin., 19 217-223 (May 3) 1944

- 127 Homans, J New England J Med, 231 51-60 (July 13) 1944
- 127a Davidson, C S and MacDonald, Harriet Am J M Sc, 205 24-33 (Jan) 1943
- 128 Quick, A J Proc Central Soc Clin Res., 16 9-10, 1943
- 128a Quick, A J Physiol Rev., 24 297 (July) 1944
- 128b Brinkhous, K M et al Am J Physiol., 125 683-687 (April) 1939
- 129 de Takats, G Surg, Gynec & Obst., 77 31-39 (July) 1943
- 130 Rhoads, J E., Walker, J and Panzer, L Northwest Med., 42 182-185 (July) 1943
- 131 Bryson, J C and Code, C F Proc Staff Meet, Mayo Clin., 19 100-108 (Feb 23) 1944
- 132 Evans, J A. New England J Med, 1 131-135 (Feb 3) 1944
- 133 de Takats, G., Trump, R A and Gilbert, N C J A M A., 125 840-845 (July 22) 1944
- 134 Kinsey, R E Arch Int Med., 73 131-137 (Feb) 1944
- 135 Murray, C K, Hale, D E. and Shaar, C M J A M A., 122 1065-1067 (Aug 14) 1943
- 136 Taylor, E S, Thalhimer, W and Cooksey, W B J A M A., 124 958-960 (April 1) 1944
- 137 Ingraham, F D and Bailey, O T J Neurosurgery, 1 23-39 (Jan) 1944
- 138 Edwards, F R Brit. M J, 1 73-76 (Jan 15) 1944
- 139 Cohn, E J et al J Clin Investigation, 23 417-432 (July) 1944
- 140 Scatchard, G, Batchelder, A C and Brown, A J Clin Investigation, 23 258-464 (July) 1944
- 141 Janeway, C A et al J Clin Investigation, 23 465-490 (July) 1944
- 142 Cournand, A et al J Clin Investigation, 23 491-505 (July) 1944
- 143 Warren, J V et al J Clin Investigation, 23 506-509 (July) 1944
- 144 National Research Council New England J Med, 231 70 (July 13) 1944
- 145 Elman, R Bull New York Acad Med., 20 220-236 (April) 1944
- 146 Hartman, A F., Lawler, H J and Mecker, C S J Pediat, 24 371 (April) 1944
- 147 Astwood, E. B J A M A., 122 78-81 (May 8) 1943
- 148 Rawson, R W et al J Clin Endocrinol., 4 1-11 (Jan) 1944
- 149 Williams, R H and Clute, H M New England J Med, 230 657-667 (June 1) 1944
- 150 Himsworth, H P Brit. M J, 1 852 (June 24) 1944
- 151 Salter, W T and Soley, M H M CLIN NORTH AMERICA, 28 484-498 (March) 1944
- 152 Williams, R H et al Endocrinology, 34 317-328 (May) 1944
- 153 Goldsmith, E. D et al J A M A., 125 847 (July 22) 1944
- 154 Spicer, S S et al Pub Health Rep, 57 1559-1566 (Oct 16) 1942
- 155 Axelrod, A E et al J Biol Chem, 148 721-722 (June) 1943
- 156 Himsworth, H P and Maizels, M Lancet, 1 959-960 (May 25) 1940
- 157 Ryan, E J and McCullagh, E P Ohio State M J., 37 430-432 (May) 1941
- 158 McLean, F C J A M A., 117 609-619 (Aug 23) 1941
- 159 Sevringhaus, E. L Am J M Sc, 203.726-731 (May) 1940
- 160 Sevringhaus, E. L and St John, R J Clin Investigation, 3 98-100 (Feb) 1943
- 161 Pope, A and Aub, J C New England J Med, 230 698-707 (June 8) 1944
- 162 Albright, F et al J Clin Investigation, 20 445 (July) 1941
- 163 Thorn, G W New England J Med., 229 33-48 (July 8) 1943
- 164 Selye, H., Hall, C E. and Rowley, E. M Canad M A J., 49 88-92 (Aug) 1943
- 165 Perera, G A et al J A M A., 125.1030-1035 (Aug 12) 1944
- 166 Huggins, C Canad M A J, 50 301-307 (April) 1944

- 167 Nesbit, R. M and Cummings R H J.A.M.A., 124 80-81 (Jan 8) 1944
- 168 Heckel N J J Clin Endocrinol., 4 168-172 (April) 1944
- 169 Bowler J P and Pedley S F New England J Med., 230 501 505 (April 27) 1944
- 170 Lyon, R A. Am. J Obst & Gynec., 47 532-536 (April) 1944
- 171 Jaeger A S and Moenning W P Urol & Cutan. Rev., 47 81-86 (Feb) 1943
- 172 Murphy J A. Am. J Obst. & Gynec., 46 146-154 (July) 1943
- 173 Roberts, H K., Loeffel E. and MacBryde, C M J.A.M.A., 123 261-264 (Oct. 2) 1943
- 174 Talisman M R Am J Obst. & Gynec., 46 534-540 (Oct) 1943
- 175 Barnes Josephine. Brit. M. J., 1 79-80 (Jan 15) 1944
- 176 Ermer J S., Mann, B and Zamostein B J Clin Endocrinol., 4 137-151 (April) 1944
- 177 McCullagh L P J Iodina State M A., 37 172-175 (April) 1944
- 178 Smith G V New England J Med., 230 339-343 (March 23) 1944
- 179 Fels, E. J Clin Endocrinol., 4 121-125 (March) 1944
- 180 Overin, P Quoted by Fels, 170
- 181 Loeser A. A. Brit. M. J., 1 479-482 (March 23) 1940
- 182 Loeser A. A. Lancet, 2 698-700 (Dec. 6) 1941
- 183 Farrow J H and Woodard H. Q J.A.M.A., 118 339-343 (Jan 31) 1942
- 184 Kochakian, C. D and Murlin J R J Nutrition, 10 437-459 (Oct.) 1935
- 185 Kochakian, C. D and Murlin J R. Am. J Physiol., 117 642-657 (Dec.) 1936
- 186 Kochakian, C. D Endocrinology 21 750-755 (Nov) 1937
- 187 Kenyon, A. T et al Endocrinology 23 135-153 (Aug) 1938
- 188 Kenyon, A. T et al Endocrinology 26 26-45 (Jan.) 1940
- 189 Kenyon, A. T et al J Clin. Endocrinol., 2 690-695 (Dec.) 1942
- 190 Albright, F et al Read before the Association for Studies of Internal Secretions, May 1941 in Atlantic City
- 191 Bassett, S. H., Keutmann, E. H and Kochakian, C. D J Clin. Endocrinol 3 400-404 (July) 1943
- 192 Dunn, J S. and McLetchie, N G B Lancet, 2 384-387 (Sept. 25) 1943
- 193 Doon, J S., Sheehan, H L. and McLetchie N G B Lancet, 1 484-4. (April 17) 1943
- 194 Hughes, H., Ware, L. L. and Young F G Lancet, 1 148-150 (Jan. 29) 1944
- 195 Goldner M G and Gomori G Proc. Soc. Exper Biol & Med., 55 73-75 (Jan) 1944
- 196 Hard, W L. and Carr C J Proc. Soc. Exper Biol & Med., 55 214-216 (Jan) 1944
- 197 Bailey C. C., Bailey O T and Leech Rachel New England J Med., 230 533-536 (May 4) 1944
- 198 Brunswick A. et al J.A.M.A., 122 966 (July 31) 1943
- 199 Brunswick A. et al J.A.M.A., 124 212-216 (Jan 22) 1944
- 200 Andrews, G B and Groat, W A New York State J Med., 40 913-917 (June 15) 1940
- 201 Duncan, G G and Barnes, C. A. Am J M. Sc., 202 553-563 (Oct.) 1941
- 202 Bailey C. C. and Marble, A. J.A.M.A., 118 683-690 (Feb 28) 1941
- 203 Bauman, L. Am J M Sci., 200 299-303 (Sept) 1940
- 204 Crombie, D W., Blaisdell, J L. and MacPherson, G Canad M A J., 50 318-328 (April) 1944
- 205 Denny and Robison Cited by Crombie et al 204
- 206 Kety S S and Letonoff T V Am. J M Sc., 205 406-414 (March) 1943
- 207 Cohen M B and Friedman H J J Allergy 14 195-202 (March) 1943

- 207 Fox, C L J A M.A., 124 207-212 (Jan 22) 1944
- 208 Rosenthal, S M Pub Health Rep., 58.513-522 (March 26) 1943
- 209 Rosenthal, S M Pub Health Rep., 58 1429-1436 (Sept 24) 1943
- 210 Harkins, H N J.A M.A , 125 533-536 (June 24) 1944
- 211 Cope, O J.A M.A , 125 536-543 (June 24) 1944
- 212 Keeney, E L Bull Johns Hopkins Hosp , 73 379-390 (Nov ) 1943

## RECENT ADVANCES IN THE TREATMENT OF TUBERCULOSIS

JULIUS L. WILSON, M.D., F.A.C.P.\*

THE most striking advances in the treatment of pulmonary tuberculosis within the past two or three years have been the introduction of chemotherapy and the continued technical refinements in thoracic surgery. In both instances the new advances are firmly based on scientific developments which preceded them in fields other than tuberculosis—another illustration of the general truth that every new method has its roots in the past. Renewed interest in the chemotherapy of tuberculosis arose with the introduction of the sulfonamides and the remarkable results obtained from the use of these drugs in other bacterial infections. Progress in thoracic surgery has been rapid and steady until it has now reached a point where the experience gained in the treatment of other conditions such as carcinoma of the lung, can now be applied to pulmonary tuberculosis.

Although the steadily declining annual mortality rates from tuberculosis and the new methods of control give reasons to believe that this disease can be practically eradicated in the course of time, this gives scant comfort to the patient with tuberculosis, and the physician must continue to treat the individual. Therefore, these newer developments in treatment offer the hope that by combined attack with chemotherapy and the necessary thoracic surgical procedure arrest of the disease in many more patients will be achieved.

### CHEMOTHERAPY

The search for a specific treatment for tuberculosis began long before the discovery of the tubercle bacillus. Vestiges of such once highly regarded remedies remain in our modern methods of treatment in the form of the common belief that milk and eggs, or even such special types as goat's milk or kumyss are specific. The use of cod liver oil has been revived on a scientific basis as an aid to nutrition rather than as an empirical remedy. Following Koch's discovery of the tubercle bacillus, many substances were tried as a specific cure—the heavy metals, iodides and other halogens, creosote and other organic products. With the repeated failure of these medications and the prevailing dogma of therapeutic nihilism there was a long period during

---

From the Division of Internal Medicine, Ochsner Clinic and the Department of Medicine, Tulane University School of Medicine, New Orleans.

\* Associate Professor of Medicine, Tulane University School of Medicine, Associate in Medicine, Ochsner Clinic.

which it was thought that tuberculosis was not amenable to chemotherapy. Even the introduction of arsenical therapy for syphilis by Ehrlich, with the resulting wave of new enthusiasm for chemotherapy, failed to produce any advance in the treatment of tuberculosis. For the past forty years it has been accepted that treatment of tuberculosis must depend on improving the general health of the patient as well as collapse therapy to close cavities and to encourage the natural process of healing. In patients suffering from the exudative, rapidly advancing forms of tuberculosis the physician has remained unable to offer more than supportive treatment.

With the announcement, in 1935, by Gerhard Domagk, of the effective treatment of streptococcal infections with prontosil (the hydrochloride of 2,4-di-amino-azobenzene-4-sulfonamide), the new era of chemotherapy began. It is unnecessary here to review the developments of other sulfonamides more specific for the pneumococcus, the meningococcus, the gonococcus and the staphylococcus. Over five thousand different chemical compounds based on the sulfonamides have been synthesized, only a few of which have been tried experimentally and clinically. The search for one of these which will act on the tubercle bacillus and the leprosy bacillus as a nontoxic, yet effective bacteriostatic agent still continues.

**Inherent Difficulties in Successful Chemotherapy**—In contrast to the acute infections produced by pyogenic organisms, there are certain inherent difficulties in the successful chemotherapy of tuberculosis by the use of a bacteriostatic or even a bactericidal agent. The first of these is the nature of the bacillus itself. The tubercle bacillus, with its lipid content, stands out among other pathogenic organisms as being notably resistant to chemical and physical agents. Because of its relatively slow rate of growth it would have to be surrounded by a bacteriostatic agent in sufficient concentration for a period of months, whereas hours or days might suffice for control of the streptococcus or the meningococcus.

Moreover, the pathologic lesion produced by the tubercle bacillus is of such a nature that it might be assumed that chemotherapeutic agents would be unable to reach the organisms effectively. The lesions are encapsulated and avascular. By experimental injections it has been shown that they are cut off from the general blood and lymphatic circulation. However, the accuracy of this view is doubtful. The observed facts that toxic substances escape and circulate and that calcium salts are regularly deposited in caseous, encapsulated tubercles indicate that the capsule is permeable to a certain extent. In 1912, Paul A. Lewis<sup>1</sup> showed that vital dyes can not only penetrate tubercles but may actually be concentrated in them. Other experimenters have demonstrated that iodides, iron and other diffusible substances readily penetrate this capsule. On the other hand, colloidal solutions do not. Whether diffusible substances can also penetrate the living cells, the

phagocytes, in which tubercle bacilli often multiply, is not so readily demonstrable

There remains one other noteworthy feature of tuberculosis which militates against successful chemotherapy. This is the chronicity and the relapsing nature of the disease. Symptoms appear months or many years after the initial infection and usually only after the disease is well advanced. Under any kind of treatment, remission, or even apparent cure, is common. Even survival and apparent good health for many years does not guarantee that the disease has healed and been arrested. Only the lasting conversion of a positive tuberculin test to negative or the actual demonstration at necropsy of healed and sterile lesions could prove the effectiveness of chemotherapy.

**Experimental Use of Sulfa Derivatives**—All of the commonly used sulfonamides and a number of their derivatives still in the experimental stage have been tried against the tubercle bacillus both in vitro and in the experimental animal. Rich and Follis<sup>2, 3</sup> found that sulfanilamide is inhibitory to the development of experimental tuberculosis in the guinea pig. Feldman and Hinshaw<sup>4</sup> reported similar results with sulfapyridine. Many other investigators noted this slight but definite effect on the course of experimental tuberculosis if the drug were given at the time of or soon after the infection had been incurred. However in human beings, no definite therapeutic effect could be noted. The well recognized toxic effects of large doses of sulfanilamide, sulfapyridine, sulfathiazole or sulfadiazine administered over a long period of time constituted a danger which outbalanced any noticeable benefit. Therefore, other more potent, more specific and less toxic compounds were sought.

In 1937, Buttle and his associates<sup>5</sup> demonstrated that diaminodiphenylsulfone was effective against many pathogenic organisms, among which was the tubercle bacillus. However, it was too toxic for clinical use. The first derivative of this preparation to be given thorough experimental trial in this country was *promin* (sodium p-p'-diaminodiphenylsulfone-N, N'-dextrose sulfonate). In 1942, Feldman, Hinshaw, Mann and Moses<sup>6, 7</sup> demonstrated that guinea pigs infected with tuberculosis and then treated with *promin* not only survived much longer than the controls but also showed definite evidences of healing upon histologic study of the lesions. Guinea pigs tolerated large daily doses of *promin* mixed with their food over a period of several months with no apparent ill effects other than a certain amount of secondary anemia. This work has been confirmed by others.

**Diasone** (disodium-formaldehyde sulfoxylate, derivative of 4-4'-diaminodiphenylsulfone) was prepared by both Bauer and Rosenthal<sup>8</sup> and Raiziss<sup>9</sup> independently in 1938. This substance retained much of its inhibiting effects on the tubercle bacillus and at the same time was much less toxic than diaminodiphenylsulfone. When used on experimental tuberculosis in guinea pigs, an effect comparable to that ob-



tained from promin was noted. As with promin, large and continuous doses of the drug were well tolerated.

**Results from the Clinical Use of Promin and Diasone in Tuberculosis in Man**—Carrying over the use of these new preparations from the experimental animal in controlled series to human beings in sanatoria has proved to be very difficult. Promin has been tried by Hinshaw, Pfuete and Feldman<sup>10</sup> with promising but not outstanding success. Human beings tolerate a relatively smaller dose of promin than guinea pigs. The disease is more entrenched and the therapeutic effect is difficult to assess. Apparently, the improvement following the use of promin is greater than can be expected from rest alone and the drug exerts an especially beneficial effect on recent and exudative lesions. Certainly, the curative effect is not pronounced. Dancey, Schmidt and Wilkie,<sup>11</sup> in a recent progress report on the treatment of human tuberculosis with promin, noted similar therapeutic effects and also observed that secondary anemia developed in all patients treated, practically all were cyanotic, over half had gastrointestinal disturbances, many had headaches, a few had albuminuria, jaundice, psychotic disturbances and rashes, and one patient had paralysis of the lower extremities. Hinshaw, Pfuete and Feldman<sup>12</sup> in another recent progress report found that fresh and exudative lesions are more responsive to promin and that the original trend of improvement has been maintained even after discontinuance of administration of the drug. Faget and his associates of the United States Public Health Service<sup>13</sup> have reported favorable results from the use of promin in leprosy. They believe that it is the most promising drug that has ever been tried for this disease.

As an unfortunate result of the tendency of our modern magazines to publicize medical and particularly therapeutic information, diasone\* (disodium formaldehyde sulfoxylate diaminodiphenylsulfone) was heralded to the public as a specific remedy some months before any scientific report of its use in treating pulmonary tuberculosis in man was available to the medical profession. Obviously played-up by the lay writer as a "sure cure for tuberculosis" and a substitute for rest treatment or collapse therapy, this premature delivery of a new drug, not yet available or accepted, disturbed countless patients and their families, who in turn annoyed their physicians. Petter and Prenzlau<sup>14</sup> then reported the results of treatment of 100 patients with this drug. They found "slight to moderate resolution" in 90 per cent of the cases. The sputum became negative within from forty-five to one hundred twenty-five days in 69 per cent of the cases. Cavities disappeared in 43 per cent of the cases. There was no control series, however, these investigators felt that this group of patients did better than similar patients with other treatment. Patients who would ordinarily have been kept in bed were allowed to be ambulant while taking diasone and any improvement was ascribed to the drug. Toxic manifestations were

\* Marketed by Abbott Laboratories

noted in a majority of the patients. All patients became anemic, over 50 per cent turned considerably cyanotic, 25 per cent has gastrointestinal disturbances, 50 per cent had headaches, 25 per cent photophobia and 12 per cent diplopia. They noted no renal damage.

The effect of both promin and diasone on experimental tuberculosis in the guinea pig was excellent and the drug was well tolerated by the animals. On the contrary, the therapeutic benefit in man was much less and the human body tolerated relatively smaller doses rather poorly. Hence, it is obvious that the experimental results in the guinea pig cannot be carried over to man. However, the efficacy of these drugs in producing healing in the guinea pig an animal most susceptible to the tuberculous infection, suggests the possibility that a sulfonamide derivative or some other drug may be found which will prove equally effective for human beings and less toxic.

### SURGICAL TREATMENT

Cavity drainage, lobectomy and pneumonectomy for pulmonary tuberculosis are now being employed in selected cases and are again under study by thoracic surgeons and phthisiologists. Neither direct drainage nor resection of the involved portion of the lungs is new. The fact is that surgical technic, better methods of closed anesthesia and our knowledge of intrathoracic physiology have only recently made possible the reasonably safe execution of the bold therapeutic conceptions of the surgeons of the 1880's and 1890's. Alexander<sup>15</sup> states that drainage of pulmonary cavities has been performed in isolated instances for centuries. As long ago as 1885 deCérenville reported a series of cases in which successful cavity drainage was performed. In 1891 Tuffier<sup>16</sup> resected an indurated tuberculous area in the pulmonary apex and the patient recovered, only to die of an acute infection seven years later. Similar attempts by other men were not so successful and Tuffier's case was long considered an isolated *tour de force*. The field of thoracic surgery had not yet been developed. However, other surgical operations for the collapse of the lung performed exterior to the thoracic cage played a large part in developing this branch of surgery. Before Forlanini introduced artificial pneumothorax, deCérenville in 1885 performed thoracoplasty to collapse the tuberculous lung. Through many modifications and improvements this operation has developed into one of the most frequently used and important methods of treating chronic cavity pulmonary tuberculosis. Phrenic nerve interruption by various operations was introduced and popularized after 1922. Localized collapse of the lesion by plombage and extrapleural pneumothorax were developed for selected cases. During this period the pleural cavity was not invaded by the surgeon except when thoracotomy was performed for empyema. It was not until the development of closed anesthesia made possible wide opening of the thorax that pneumonectomy could be undertaken for carcinoma of the lung.

and lobectomy for bronchiectasis and other suppurative lesions. The successful surgical attack on these conditions, plus the skill required and the improved knowledge of pulmonary physiology, brought about a revival of interest in pulmonary resection for tuberculosis.

Two related observations in the study of cases of pulmonary tuberculosis in which the ordinary methods of collapse therapy fail to close the cavities or to produce sputum negative for tubercle bacilli have stimulated the search for a more satisfactory method of treatment in such instances. The first of these is the "tension cavity." Therapeutic pneumothorax with external pneumonolysis may fail to close these cavities. Similarly, a technically excellent thoracoplasty may fail. The second observation is that up to 10 or 15 per cent of cases of cavitory pulmonary tuberculosis may also have tracheobronchial tuberculosis. In these, collapse of the lung by therapeutic pneumothorax may be positively harmful and thoracoplasty may fail to render the sputum negative for tubercle bacilli. These two observations are related by the fact that involvement of the bronchus draining a cavity may produce incomplete bronchial stenosis which in turn leads to overinflation of the cavity. The treatment of tuberculosis of the bronchial tree itself remains an unsolved problem.

**Treatment of the Tension Cavity**—The tension cavity may be treated in one of two ways: either drainage of the cavity to the exterior or in certain cases, resection of the lung or portion of the lung in which the cavity lies.

**Cavernostomy**—Drainage of the cavity to the exterior can be carried out either by the method of Monaldi<sup>17</sup> with prolonged aspiration or by directly opening the cavity to the exterior—"cavernostomy." Monaldi's method of cavity drainage has been widely tried, both in Europe and in this country, since its introduction in 1939. Although it is capable of reducing the size of tension cavities, they tend to reopen promptly when the catheter is removed. Some other form of collapse therapy, usually a thoracoplasty, must then be done at once. Naturally, obliteration of the pleural space is a prerequisite. As the operation is more or less blind, there is serious danger of massive hemorrhage at the time of introduction of the cannula, in most instances the patients react with considerable elevation of temperature due to the introduction of secondary infection, and finally there is apt to be persistent fistulous formation through the thoracic wall. The procedure is essentially unphysiologic. For cavernostomy the pleural space must also be previously obliterated, the cavity must be against the pleura in an accessible location, and other cavities or progressive disease must be absent in that and in the contralateral lung. As a rule the operation is indicated only when other measures of collapse, including thoracoplasty, have been unsuccessful. If thoracoplasty has been performed, and a cavity of the tension type prevents effective collapse, the choice of the surgeon may lie between a revision operation and cavernostomy.

In many such cases revision is most difficult and often unsuccessful. It is these instances that present the best indication for cavernostomy. Eloesser<sup>18</sup> and Shipman, Rogers and Daniels<sup>19</sup> have described a skin flap operation for surgical drainage of such cavities. It is probable that such an operation will be more widely used in the future.

*Pulmonary Resection*—The second method of treating the tension cavity resisting other forms of therapy is pulmonary resection. Since lobectomy, or even pneumonectomy of a nonadherent lung is a simpler operation than a two or three stage thoracoplasty, there is a temptation to substitute one of these radical methods of resection for other measures of collapse therapy. However, pulmonary tuberculosis in the stages severe enough to require major surgical procedures is seldom confined to one lobe or even to one lung and, of course the lesion here is only a manifestation of a generalized disease. Therefore, lobectomy or pneumonectomy for tuberculosis should be limited to cases with certain definite indications. These are primarily the cases with tuberculous bronchitis producing bronchial stenosis and either large tension cavities or pulmonary suppuration distal to the bronchial obstruction. The operation may also be indicated in cases in which thoracoplasty has been performed with failure to close cavities for control of the disease in the lung, and in some of the rare instances of isolated cavities in the lower lobe where thoracoplasty might sacrifice the healthy upper lobe and other means of collapse might have already failed. In any case, there should not be active disease in the contralateral lung. Dolley and Jones<sup>20, 21</sup> recorded their experiences with this method of treatment in 1939 and 1940. Churchill and Klopstock<sup>22</sup> reported several cases and reviewed the subject in 1943. Alexander<sup>23</sup> has discussed the role of pneumonectomy and thoracoplasty in the treatment of cases with bronchial stenosis. As the procedure is still in its experimental stage, it is too early to comment on the results other than to say that, with the utmost skill of the surgical team, properly selected patients have an excellent chance of recovery. With more experience and with a strict limitation to definite indications it is probable that pulmonary resection for pulmonary tuberculosis will tend to take a definite place in the armamentarium of treatment. Probably not more than 1 or 2 per cent of cases will require this type of operation.

### CONCLUSIONS

- 1 The results of chemotherapy of experimental tuberculosis in the guinea pig justify the hope that human tuberculosis, particularly in acute and exudative forms, may be amenable to treatment by similar means.

- 2 The sulfonamide derivatives thus far tried on human beings have been too toxic for general clinical use.

- 3 If drugs can be found which are safe and effective against tuberculosis in the guinea pig there is no reason why other drugs cannot be

discovered to accomplish the same results in tuberculosis of human beings

4 The problem of treating cases of pulmonary tuberculosis resistant to collapse therapy because of bronchostenosis and tension cavities may be solved in some instances either by cavernostomy or by pulmonary resection

5. The combination of chemotherapy and thoracic surgery offers great hope of a more successful treatment of pulmonary tuberculosis in the future

#### BIBLIOGRAPHY

- 1 Lewis, P A Arch Int Med, 10 68-70, 1912
- 2 Rich, A R. and Follis, R H, Jr Bull Johns Hopkins Hosp, 62 77-84 (Jan) 1938
- 3 Follis, R H, Jr and Rich, A R Ibid, 65 466-488 (Dec) 1939
- 4 Feldman, W H and Hinshaw, H C Proc Staff Meet., Mayo Clin, 14 174 176 (March 15) 1939
- 5 Buttle, G A H., Stephenson, D, Smith, S., Dewing, T and Foster, G E Lancet, 1 1331-1334 (June 5) 1937
- 6 Feldman, W H, Hinshaw, H C and Moses, H E Am Rev Tuberc., 45 303-333 (March) 1942
- 7 Feldman, W H, Mann, F C and Hinshaw, H C Am Rev Tuberc., 46 187-195 (Aug) 1942
- 8 Bauer, H and Rosenthal, S M Pub Health Rep, 53 40-49 (Jan 14) 1938
- 9 Raiziss, G W Science, 98 350 (Oct 15) 1943
- 10 Hinshaw, H C, Pfuertze, K. and Feldman, W H Am Rev Tuberc., 47 26-34 (Jan) 1943
- 11 Dancey, R J, Schmidt, R H and Wilkie, J M Ibid, 49 510-534 (June) 1944
- 12 Hinshaw, H C, Pfuertze, K and Feldman, W H Ibid, 50 52-57 (July) 1944
- 13 Faget, G H, Pogge, R C, Johansen, F A., Dinan, J F., Prejean, B M and Eccles, C G Pub Health Rep, 58 1729-1741 (Nov 26) 1943
- 14 Petter, C K and Prenzlau, W S Am Rev Tuberc., 49 308-322 (April) 1944
- 15 Alexander, John The Collapse Therapy of Pulmonary Tuberculosis Springfield, Ill., Charles C Thomas, 1937
- 16 Tuffier, T État actuel de la chirurgie intrathoracique Paris, Masson et Cie, 1914, pp 90-105
- 17 Monaldi, V Sett med., 27.231-246 (Feb 23) 1939
- 18 Eloesser, L J Thoracic Surg, 10 501-528 (June) 1941
- 19 Shipman, S J, Rogers, W L and Daniels, A C Am Rev Tuberc., 44 588-595 (Nov) 1941
- 20 Jones, J C and Dolley, F S J Thoracic Surg, 8 351-370 (April) 1939
- 21 Dolley, F S and Jones, J C Ibid, 10 102-121 (Oct) 1940
- 22 Churchill, E D and Klopstock, R Ann Surg., 117 641-669 (May) 1943
- 23 Alexander, J Am Rev Tuberc., 44 765-767 (Dec) 1941

## SOME RECENT ADVANCES IN BRONCHIAL ASTHMA

VINCENT J. DERBES, M.D.\*

### IMMUNOLOGIC CONSIDERATIONS

ALLERGIC bronchial asthma results from the interaction of antigens (foods, pollens, dusts) and antibodies, mediating or effector substances being brought into play. In a recent study Cannon<sup>1</sup> directs attention to the fact that these antibodies have been shown to be modified serum globulins with definitely established chemical compositions. They are produced, in all likelihood, from globulin and are synthesized in stereochemical relationship to the antigen for which they have a specific affinity. This synthesis is modified by the "templating action" of the absorbed antigen. The "antigenic template" is synthesized for the intracellular protein reserves. A wide variety of cells is involved in this process, but especially those of the reticuloendothelial system. Since antibody globulin is specifically modified normal globulin, the mechanism of antibody formation is closely related to that of globulin production. Cannon<sup>1</sup> further shows that the effectiveness of globulin synthesis, and therefore antibody production, is determined by the quality and quantity of globulin reserve continuously available.

It is generally accepted today that these antibodies may be free in the blood stream or attached to tissue cells that is, sessile. Interaction of antigen and antibody in the blood stream is not productive of clinical disease but symptoms may follow coupling of sessile antibodies and antigen. There is a certain amount of evidence to show that histamine may be the mediating or effector substance. Thus, Katz and Cohen<sup>2</sup> were able to show that there was definite liberation of histamine when red blood cells from persons sensitive to ragweed were 'shocked' in vitro. Furthermore, histamine causes smooth muscle to contract. On the other hand, Rose's<sup>3</sup> studies on histamine in patients with allergy do not warrant the conclusion that histamine is released during the attack. Urbach and Gottlieb<sup>4</sup> have summarized the data supporting the view that perhaps acetylcholine is the substance which mediates anaphylaxis or allergy. All allergic manifestations can be reproduced when this substance is used to stimulate the parasympathetic nerves. The injection of acetylcholine will cause an attack of asthma in an asthmatic patient, this has been suggested as a means of differentiating between cardiac and bronchial asthma. Wenner and Buhr-

---

From the Section on Allergy, Ochsner Clinic and the Department of Medicine, Tulane University School of Medicine, New Orleans.

Instructor in Medicine and Preventive Medicine and Director of Allergy Clinic, Tulane University School of Medicine. Director of Allergy Section, Ochsner Clinic, New Orleans.

mester<sup>5</sup> showed that the acetylcholine content of the blood is increased in patients with asthma Urbach and Gottlieb<sup>4</sup> have reported successful results in selected patients with asthma treated with small doses of acetyl- $\beta$ -methylcholine chloride (mecholyl) At the present time it seems probable that no one chemical is involved but rather that several biologically active substances, including histamine, acetylcholine and probably epinephrine, take part in the precipitation and continuation of the asthmatic paroxysm

The excellent work of Cooke<sup>6</sup> and his school is leading to clarification of a troublesome question Why should parenteral therapy with ragweed pollen, for example, desensitize a patient, when repeated exposure to the same antigen through the bronchial mucosa results in asthma? Cooke and his associates have presented evidence tending to show that antibodies appearing in the serum of treated persons (allergic or not) are not the same as those appearing from the hypersensitivity itself The one is thermolabile and skin sensitizing and is demonstrated by skin testing The other, which results from specific desensitization, is not capable of sensitizing recipients and is thermostable This latter antibody blocks or neutralizes the antigen before it can interact with the sessile antibody in the bronchiole Loveless<sup>7</sup> has shown that there is a decrease, at a fairly rapid rate, of the blocking antibody after therapy has been discontinued

#### PATHOLOGIC CONSIDERATIONS

Lamson, Butt and Stickler<sup>8</sup> have reported their clinical and post mortem findings in eighty-two adults and four children with "fatal asthma" They could find no evidence of general lymphoid hyperplasia in the four children studied The average age at death in the women was 46.2 years and 55 years in the men The average duration of dyspnea was nineteen years in the women and thirty years in the men It was found that the symptoms of asthma were stimulated by a wide variety of conditions including pronounced interstitial emphysema, extensive atelectasis, pulmonary fibrosis, bronchiectasis, rheumatic heart disease of long standing, hypertension and syphilitic aortitis Since many patients in this series died shortly after the use of morphine sulfate, Lamson and his co-workers advise against the use of this drug or similar depressants in cases of bronchial asthma Vaughan and Graham<sup>9</sup> have also emphasized the dangers associated with the use of opiates in patients suffering from severe attacks of bronchial asthma They point out that opiates depress the respiratory center and also have a slight bronchospastic effect They believe that the sicker the patient the greater the danger from the use of opiates, in their experience death from acute intractable asthma is rare Lamson, Butt and Stickler<sup>8</sup> are in accord with the conclusion of Tuft<sup>10</sup> that "there is at present no known pathologic picture, either gross or microscopic, which may be considered characteristic or pathognomonic of asthma"

This last view is somewhat at variance with that expressed by Hilding,<sup>11</sup> who believes that the importance of the role of the ciliary mechanism in diseases of the lower respiratory tract, such as asthma and bronchiectasis, has been underestimated. The removal of secretions from the lower respiratory tract is largely dependent on ciliary action. Hilding<sup>11</sup> analyzed the records and pathologic material from thirty-nine cases of fatal asthma, twelve cases of influenza and ten cases of bronchopneumonia. The most characteristic findings were the changes in the bronchial epithelium. Metamorphosis has occurred and goblet-like cells had replaced the normal columnar ciliated cells. The ciliary mechanism was apparently lost and a viscid mucinous secretion blocked the air passages and was adherent to the walls. The gradual occlusion of the air passages eventually caused death from asphyxia. Hilding<sup>11</sup> believes that the most important pathologic change in asthma is the loss of ciliary function and that this is the principal cause of death in these cases. Experimental work in rabbits in which attempts were made to study the effects of destroying the ciliated epithelium of the bronchi has not proved satisfactory thus far. Bases and Kurtin<sup>12</sup> made a plea for the use of bronchoscopy and suction as a means of removing obstructing secretions. This position is also held by Hilding,<sup>11</sup> who suggests that mechanical removal of the secretions by aspiration through a bronchoscope or by tracheotomy should be resorted to as a life saving measure in cases of apparently severe bronchial obstruction by viscid secretions.

#### THE ASTHMATIC SOLDIER AND THE ARMY

Major R. I. Alford<sup>13</sup> has recently published an interesting study from a large general hospital on military experience with patients who have bronchial asthma. Although it might seem strange at first that men with bronchial asthma are inducted into the Army, Alford found from a survey of such cases that there was sufficient reason for their induction. Since the history of asthma without confirming physical signs is insufficient grounds for rejection, many were inducted during a period of freedom of symptoms. Others, anxious to join the Army, did not reveal their allergic condition. Furthermore, men with asthma were often accepted because of the pressure exerted on induction boards to fill their quota. Some medical examiners told these inductees that a change of climate would be of benefit or that medical officers would take care of them.

Alford<sup>13</sup> points out that asthma developed for the first time in some men when they encountered new and powerful, offending agents. Although it is felt that men with bronchial asthma have little or no place in the Army, an effort is still made to salvage men in order to utilize all available manpower. Under the leadership of Colonel S. W. French and Major L. J. Halpin<sup>14</sup> almost every large military hospital has an allergy clinic and extracts are prepared and distributed to other mili-



mester<sup>5</sup> showed that the acetylcholine content of the blood is increased in patients with asthma Urbach and Gottlieb<sup>4</sup> have reported successful results in selected patients with asthma treated with small doses of acetyl- $\beta$ -methylcholine chloride (mecholy) At the present time it seems probable that no one chemical is involved but rather that several biologically active substances, including histamine, acetylcholine and probably epinephrine, take part in the precipitation and continuation of the asthmatic paroxysm

The excellent work of Cooke<sup>6</sup> and his school is leading to clarification of a troublesome question Why should parenteral therapy with ragweed pollen, for example, desensitize a patient, when repeated exposure to the same antigen through the bronchial mucosa results in asthma? Cooke and his associates have presented evidence tending to show that antibodies appearing in the serum of treated persons (allergic or not) are not the same as those appearing from the hypersensitivity itself The one is thermolabile and skin sensitizing and is demonstrated by skin testing The other, which results from specific desensitization, is not capable of sensitizing recipients and is thermostable This latter antibody blocks or neutralizes the antigen before it can interact with the sessile antibody in the bronchiole Loveless<sup>7</sup> has shown that there is a decrease, at a fairly rapid rate, of the blocking antibody after therapy has been discontinued

#### PATHOLOGIC CONSIDERATIONS

Lamson, Butt and Stickler<sup>8</sup> have reported their clinical and post mortem findings in eighty-two adults and four children with "fatal asthma" They could find no evidence of general lymphoid hyperplasia in the four children studied The average age at death in the women was 46.2 years and 55 years in the men The average duration of dyspnea was nineteen years in the women and thirty years in the men It was found that the symptoms of asthma were stimulated by a wide variety of conditions including pronounced interstitial emphysema, extensive atelectasis, pulmonary fibrosis, bronchiectasis, rheumatic heart disease of long standing, hypertension and syphilitic aortitis Since many patients in this series died shortly after the use of morphine sulfate, Lamson and his co-workers advise against the use of this drug or similar depressants in cases of bronchial asthma Vaughan and Graham<sup>9</sup> have also emphasized the dangers associated with the use of opiates in patients suffering from severe attacks of bronchial asthma They point out that opiates depress the respiratory center and also have a slight bronchospastic effect They believe that the sicker the patient the greater the danger from the use of opiates, in their experience death from acute intractable asthma is rare Lamson, Butt and Stickler<sup>8</sup> are in accord with the conclusion of Tuft<sup>10</sup> that "there is at present no known pathologic picture, either gross or microscopic, which may be considered characteristic or pathognomonic of asthma"

This last view is somewhat at variance with that expressed by Hilding,<sup>11</sup> who believes that the importance of the role of the ciliary mechanism in diseases of the lower respiratory tract, such as asthma and bronchiectasis, has been underestimated. The removal of secretions from the lower respiratory tract is largely dependent on ciliary action. Hilding<sup>11</sup> analyzed the records and pathologic material from thirty-nine cases of fatal asthma, twelve cases of influenza and ten cases of bronchopneumonia. The most characteristic findings were the changes in the bronchial epithelium. Metamorphosis has occurred and goblet-like cells had replaced the normal columnar ciliated cells. The ciliary mechanism was apparently lost and a viscid mucinous secretion blocked the air passages and was adherent to the walls. The gradual occlusion of the air passages eventually caused death from asphyxia. Hilding<sup>11</sup> believes that the most important pathologic change in asthma is the loss of ciliary function and that this is the principal cause of death in these cases. Experimental work in rabbits in which attempts were made to study the effects of destroying the ciliated epithelium of the bronchi has not proved satisfactory thus far. Bases and Kurtin<sup>12</sup> made a plea for the use of bronchoscopy and suction as a means of removing obstructing secretions. This position is also held by Hilding,<sup>11</sup> who suggests that mechanical removal of the secretions by aspiration through a bronchoscope or by tracheotomy should be resorted to as a life saving measure in cases of apparently severe bronchial obstruction by viscid secretions.

#### THE ASTHMATIC SOLDIER AND THE ARMY

Major R. I. Alford<sup>13</sup> has recently published an interesting study from a large general hospital on military experience with patients who have bronchial asthma. Although it might seem strange at first that men with bronchial asthma are inducted into the Army, Alford found from a survey of such cases that there was sufficient reason for their induction. Since the history of asthma without confirming physical signs is insufficient grounds for rejection, many were inducted during a period of freedom of symptoms. Others, anxious to join the Army did not reveal their allergic condition. Furthermore, men with asthma were often accepted because of the pressure exerted on induction boards to fill their quota. Some medical examiners told these inductees that a change of climate would be of benefit or that medical officers would take care of them.

Alford<sup>13</sup> points out that asthma developed for the first time in some men when they encountered new and powerful, offending agents. Although it is felt that men with bronchial asthma have little or no place in the Army, an effort is still made to salvage men in order to utilize all available manpower. Under the leadership of Colonel S. W. French and Major L. J. Halpin<sup>14</sup> almost every large military hospital has an allergy clinic and extracts are prepared and distributed to other mili-

tary hospitals from the Laboratory of the Fourth Service Command. Analysis of the first hundred cases at Percy Jones General Hospital reveals that 71 per cent of patients were discharged and 29 per cent were returned to limited duty.

Alford<sup>18</sup> calls attention to the fact that the disposition board is frequently handicapped in the ultimate fulfillment of its function by the varied conception of nonstrenuous duty by other officers. Thus, one patient on limited duty was doing strenuous exercise as a dock worker unloading ships, another had done well as a cook until he was given commando training, a sergeant, already on limited duty, was put in charge of a cleaning detail, which was the dustiest work on the post. Alford concludes that men with active bronchial asthma should not be inducted into the Army because it is impossible to give a soldier the same environmental protection against dust, molds, pollens, foods or dampness that he can have in civilian life.

#### UNUSUAL COMPLICATIONS

**Rib Fractures**—Oechsli<sup>15</sup> has reported fracture of the ribs due to cough in bronchial asthma. The position of the fractures is of considerable interest from the standpoint of mechanism of its production. Oechsli found in his own cases, and those reported, that without exception the fractures are in a line extending from a point about 4 cm from the costochondral articulation of the fourth rib obliquely caudad and lateral to the ninth rib in the midaxilla. In Figure 84 the four fractured ribs can be seen to lie in this same line. Oechsli<sup>15</sup> called attention to the fact that this location corresponds to the heavy muscular attachments of the external abdominal oblique muscle at its interdigitation with the serratus anterior muscle. It is probable that contraction of the abdominal expiratory muscles alone is not the sole cause of fracture. Analysis of previous cases indicated that in all instances the muscles attached to the shoulder girdle and the thoracic wall were tense at the same time that the abdominal muscles were in strong contraction in the expiratory phase of coughing.

**Pulmonary Rupture**—Derbes, Engelhardt and Sodeman<sup>16</sup> have presented a study of the consequences of pulmonary rupture in the asthmatic patient. After a pulmonary tear the course taken by the freed air determines whether there will be a subcutaneous emphysema, spontaneous pneumothorax, mediastinal emphysema or a combination of any of these. In view of the pronounced thinning of the alveolar walls and increase in intra-alveolar pressure so often present in chronic asthma, these complications should occur frequently, but this does not seem to be the case. In pneumothorax the findings are the same as those seen in uncomplicated instances except that the characteristic signs of bronchial asthma are often superimposed. Among the outstanding symptoms are pain, dyspnea, cough and collapse. There is generally a decrease in tactile fremitus and breath and voice sounds. Hyperresonance

nance together with displacement of the heart and mediastinal structures to the unaffected side may be demonstrated. The outstanding finding of mediastinal emphysema is a peculiar, loud, crackling, bubbling sound which is synchronous with the heart beat. Severe pain not unlike that of coronary occlusion, may be present. Hamman<sup>17</sup> had described several differential features: absence of constitutional symptoms and evidence of shock, normal temperature and lack of change in the blood pressure and leukocyte count.

We<sup>18</sup> have shown that subcutaneous emphysema may involve not only the neck but may extend to the face, upper extremities, thorax and



Fig. 84—Roentgenogram of chest showing four fractured ribs with callus formation

abdomen. These complications are believed to be secondary to the rupture of a valvular vesicle which is so constructed that air enters more readily than it leaves.<sup>18</sup> We<sup>18</sup> believe that the physician should exercise restraint in the use of mechanical measures because the nature of the lesion is such that with little or no treatment the majority of patients completely recover. Tapping and removal of the escaped air is frowned upon because it disturbs a protective mechanism, namely the equality of pressure on either side of the alveolus. This pressure equality allows for a minimum of movement and maximum healing. Bed rest for about a month and sedatives as needed are thought to be

the most important points in the treatment Thoracentesis should be reserved for those cases of tension pneumothorax in which the intra pleural pressure is such as to embarrass seriously the patient's respiration

### TREATMENT

**Medical Treatment**—A certain amount of the dyspnea of asthma is due to tenacious sputum and the value of expectorants has long been recognized Two interesting studies on sputum have been made by Basch, Holinger and Poncher<sup>19, 20</sup> They were able to show that sputum could be divided physically and chemically into three types These types are not to be confused with the three layers into which sputum of patients with bronchiectasis separates on standing The first portion of the sputum coughed up, which is the highest in the bronchial tree, is a bronchial mucous plug This is a pathologic product of high viscosity and is the result of changes caused by drying The third part is found in the most dependent portions of the bronchial tree. Basch and his co-workers were able to obtain this portion only by bronchoscopic aspiration This sputum has an extremely high viscosity and a high content of organic and inorganic substances The second portion of the sputum is a diluted liquefied fraction which has a lower viscosity than the third portion from which it arises by means of cough, ciliary action and the pressure of secretions Liquefaction of the sputum may be the result of the secretion of liquid substances into the sputum, the resorption of solid substances or the result of bacterial or enzymatic liquefaction

The second part of the study conducted by Basch, Holinger and Poncher<sup>20</sup> was concerned with the influence of therapeutic agents They found that the *expectorant drugs*, ammonium chloride, potassium iodide, fluid extract of ipecac and emetine hydrochloride, consistently liquefied the sputum of patients with bronchiectasis, as evidenced by a decrease in the measured viscosity No differences were noted in the relative efficacy of these drugs with regard to liquefaction Reference may be made at this point to the study of Tuft and Levin<sup>21</sup> They gave patients iodides intravenously and orally in an attempt to study the expectorant action of this drug Bronchoscopy was performed on each patient and specimens of secretions were obtained at regular intervals following the administration of the drug. The results indicated that iodides are excreted in the bronchi After intravenous injection an interval of between fifteen and twenty-five minutes elapsed before the iodides appeared in the bronchial secretion The appearance of the drug in the sputum was slightly delayed after oral administration From the point of view of expectorant properties these authors found that the intravenous administration of iodides holds little advantage over the oral route

Basch and his co-workers<sup>19, 20</sup> found that the *inhalation of steam* liquefied the sputum more effectively than did the expectorant drugs

This liquefaction is the result of a reduction in the content of organic and inorganic substances. They found the inhalation of *carbon dioxide* to be an extremely effective expectorant. Such inhalations seem to reduce the amount of sputum within the bronchial tree by stimulating resorption and rendering the remainder more liquid so that it is coughed up more easily. They considered the most effective therapeutic regimen to clear the bronchial tree of pathologic secretions to be a combination of inhalation of steam and carbon dioxide and the administration of expectorant drugs. Unfavorable effects were observed from oxygen inhalation in that it greatly increased both the viscosity of the sputum and its content of solid substances. Codeine sulfate also increased the viscosity of the sputum and ought not to be used with an expectorant if dilution of the sputum is the therapeutic objective. Atropine sulfate was found to act as an anti-expectorant by decreasing the production of sputum and considerably increasing its viscosity.

Maietta<sup>22</sup> recommends the use of *ether in oil intramuscularly* in the treatment of bronchial asthma. He reports that the intramuscular injection of 2-cc. doses of a mixture of equal parts of ether and peanut oil produces relief in stubborn cases of bronchial asthma. The immediate effects were transient and unimportant. The taste and smell of ether are immediately perceived and may last a day. Although the injection caused a temporary burning pain, neither induration nor abscess resulted. A few hours later, Maietta's patients were quieter because of the sedative effect and they breathed more easily. The ether excreted in the lungs loosened the mucous plug and favored expectoration. Epinephrine-fast patients were found to respond again. Doses of 2 cc. of ether in oil may be repeated in several hours if indicated.

Shulman<sup>3</sup> has written enthusiastically about the use of *sodium 5,5-diphenyl-hydantoinate* (dilantin sodium) in bronchial asthma. He was led to use this drug after recognizing the psychogenic aspect of some cases. Seven children with intractable nonseasonal asthma were treated continuously with doses of 0.1 to 0.2 gm daily. Other anti-allergic measures were suspended during the period of investigation. Six of the seven patients were observed for a period of from six to twelve months and were almost free of asthma during this period, even following respiratory infections and emotional upsets. Patients with seasonal allergies were unaffected.

Not all of the newer drugs receive favorable mention. Thus, Logue and Laws<sup>24</sup> reported an attempt to develop tolerance to *mecholy*l or to increase the production of cholinesterase by the administration of increasing doses of mecholy. A control series of asthmatic victims receive injections of physiologic saline solution. In the group receiving mecholy. 54 per cent improved, whereas 66 per cent of the controls were better. They concluded that mecholy. is of little value in the hyposensitization of patients with asthma.

*Histamine azoprotein complex*\* has definite possibilities and will be discussed in some detail. By diazotization Fell, Rodney and Marshall<sup>25</sup> combined histamine with despeciated horse serum globulin to form an antigen complex in which histamine acted as a hapten. Guinea pigs and rabbits immunized with histamine azoprotein and sensitized to crystalline ovalbumin were more resistant to a shocking dose of crystalline ovalbumin than nonimmunized controls. It was concluded from these experiments that immunization with histamine azoprotein renders animals resistant to anaphylaxis. Following up this work, Cohen and Friedman<sup>26</sup> injected a group of patients with chronic urticaria, atopic dermatitis and vasomotor rhinitis. They began with 0.05 cc of histamine azoprotein and increased this to 1.5 cc at three to seven day intervals over a period of from three months to one year. Precipitin studies in which the collodion particle technic performed on sera taken previous to treatment was employed, yielded negative results whereas those on sera taken after treatment showed the presence of precipitins to the injected complex. Further studies revealed this precipitin to be specific for the histamine portion of the compound. Iontophoretic studies demonstrated that sera containing histamine antibodies were capable of neutralizing histamine to a variable degree. Sheldon, Fell, Johnston and Howes<sup>27</sup> reported favorable clinical results in a variety of allergic disorders. I have been favorably impressed by the use of histamine azoprotein in a series of seventeen asthmatic patients observed over a period of approximately four months.

Ruskin<sup>28</sup> studied the influence of *vitamin C* on the antihistamine action of various drugs. Sections from the bronchioles of rabbits' lungs were prepared by a special technic permitting microscopic observation. Histamine was used to produce bronchoconstriction and then another drug was added. Drugs antagonistic to histamine permitted the constricted bronchioles to relax. Ascorbic acid did not hasten recovery from histamine contraction but when serving as the acid radical for calcium, ephedrine, benzedrine or epinephrine, it was a histamine antagonist and bronchodilator.

Several papers on *inhalation therapy* have appeared. Westcott and Gillson<sup>29</sup> believe that most ambulatory asthmatic patients, and some who are bedridden, can perform simple mechanical breathing exercises which results in some increase in vital capacity. A substantial increase in vital capacity and a proportionally greater subjective relief from symptoms follows the use of inhalation therapy with 1:100 epinephrine combined with regular breathing exercises and postural drainage when these measures are indicated. Dryness and irritation of the throat are among the most frequent untoward effects observed following the use of 1:100 epinephrine solution either by the continuous inhalation method or the bulb vaporizer method. Lockey<sup>30</sup> states that these symp-

\* Marketed by Parke-Davis under the trade name of hapamine.

toms often disappear if the patient swallows a few drams of warm glycerin immediately after inhalation of epinephrine. He modified the 1:100 epinephrine hydrochloride solution by incorporating 5 per cent glycerin in it. Clinical trials revealed that irritation and dryness of the throat occurred less frequently in 82 per cent of cases among the patients using glycerinized epinephrine solution than among those using the unmodified epinephrine solution.

Barach<sup>31</sup> maintains that repeated relaxation of spastically contracted circular bronchial muscle over a five to ten day period is apt to result in prolonged freedom from severe asthma. His plan of treatment in hospitalized patients consists of immediate rectal injection of aminophylline in water, followed by the inhalation of a spray of 0.5 cc. of 1:100 epinephrine vaporized by oxygen under high pressure. Some patients receive in addition a spray of 1 per cent neosynephrin hydrochloride. Excitable patients receive hypodermic injections of dilaudid. Following these procedures the patients are placed in a helium-oxygen hood for two hours. Another rectal instillation of aminophylline is given before bedtime, sometimes combined with dilaudid. The entire routine is continued for a period of five days and the rectal injection of aminophylline is continued at home. After discharge from the hospital a saturated solution of potassium iodide in doses of 1 cc. is administered three times daily. The duration of improvement varied from one week to more than a year. Barach<sup>31</sup> concludes that repeated bronchial relaxation may be achieved by a combination of helium therapy and aminophylline and that this procedure is of great value in terminating status asthmaticus.

### SURGICAL TREATMENT

Gay and Rinehoff<sup>32</sup> report further observations on the treatment of intractable bronchial asthma by *bilateral resection of the pulmonary plexus*. This operation is to be considered only when all other therapeutic measures have been employed without success. All the cases reported were severe chronic intractable asthma of the intrinsic type with chronic pulmonary infection. The age of the patient and the duration of the asthma were of less significance in the outcome than the amount of pulmonary disease present at the time of operation. Inasmuch as these patients were poor operative risks a high mortality rate resulted (nine deaths in twenty-one cases). Of the remainder eight patients were considerably improved after a short period during which the secondary pulmonary disease subsided.

The question arises as to how good a surgical risk is the asthmatic patient. Gaarde, Prickman and Raskowski<sup>33</sup> reviewed 180 consecutive cases of allergic asthma and asthmatic bronchitis in which major operations had been performed. All of these cases had received careful pre-operative and postoperative allergic care. In twenty-five of the cases (13 per cent) some form of pulmonary complication developed fol-



lowing operation Pneumonia, bronchitis and severe asthma were the most common complications encountered The incidence of pulmonary complications was about equal in patients with allergic asthma and asthmatic bronchitis When postoperative asthma was excluded as a complication, pulmonary complications were about three times as frequent after upper abdominal operations than after lower abdominal procedures Among the general population, the incidence of pulmonary complications following operations on the upper part of the abdomen is approximately twice that of those following operations on the lower part of the abdomen It seemed, therefore, that although asthmatic patients tended to show an increased incidence of postoperative complications following operations on the upper part of the abdomen, the incidence of complications in the group as a whole was not greatly increased

### PROGNOSIS

What may be expected from the treatment of bronchial asthma? Unger and Wolf,<sup>34</sup> who followed 207 cases of bronchial asthma for seven years, observed that those patients who had been free of symptoms when previously examined were still progressing satisfactorily Two hundred and fifty-two additional cases were studied They were divided into two groups—paroxysmal and chronic asthma The best therapeutic results were obtained among the patients in the paroxysmal group, especially among those whose symptoms were caused by known allergens which could be eliminated A high percentage of these patients began to manifest symptoms in the first decade of life The mortality rate in the entire series was about 10 per cent

### BIBLIOGRAPHY

- 1 Cannon, P R J Lab & Clin Med., 28 127-139 (Nov) 1942
- 2 Katz, G and Cohen, S J.A.M.A., 117 1782-1783 (Nov 22) 1941
- 3 Rose, B J Clin Investigation 20 419-428 (July) 1941
- 4 Urbach, E and Gottlieb, P N Allergy New York, Grune & Stratton, 1943
- 5 Wenner, W L and Buhrmester, Catherine C J Allergy, 9:85-90 (Nov) 1937
- 6 (a) Cooke, R A., Barnard, J H, Hebal, S and Stull, A J Exper Med., 62 733-750 (Dec) 1935
- (b) Cooke, R A., Loveless, M and Stull, A J Exper Med, 66 689-696 (Dec) 1937
- 7 Loveless, M H J Immunol., 38 25-50 (Jan) 1940
- 8 Lamson, R W, Butt, E. M and Stuckler, M J Allergy, 14 396-413 (July) 1943
- 9 Vaughan, W T and Graham, W R J.A.M.A., 119 556-557 (June 13) 1942
- 10 Tuft, Louis Clinical Allergy Philadelphia, W B Saunders Co, 1937
- 11 Hilding, A C. Tr Am Acad Ophth (1942), 47 376-393 (May-June) 1943
- 12 Bases, L and Kurtin, A Arch Otolaryng., 56 79-85 (July) 1942
- 13 Alford, R. I J Allergy, 15 196-202 (May) 1944
- 14 French, S W and Halpin, L J Ann Allergy, 1 1-16 (July-Aug) 1943
- 15 Occhsl, W R J Thoracic Surg., 5 530-534 (June) 1936

16. Derbes V J., Engelhardt, H T and Sodeman, W A. *Ann. Allergy* (In Press.)
17. Hamman, L. *Bull Johns Hopkins Hosp.*, 64 1-21 (Jan) 1939
18. Kjaergaard, H. *Acta Med Scandm.*, 43 (Suppl) 1, 1932 and 86-93, 1933
19. Basch, F P., Holinger P and Poncher H G. *Am J Dis Child.*, 62-981-990 (Nov) 1941
20. Basch, F P., Holinger, P and Poncher H G. *Am J Dis Child.*, 62 1149-1171 (Dec.) 1941
21. Tuft, L. and Levin, N M. *Am J M Sc.*, 203 717-722 (May) 1942
22. Maietta, A. L. *New England J Med.*, 227-985-987 (Dec. 24) 1942
23. Shulman, M H. *New England J Med.*, 226 260-264 (Feb 12) 1942
24. Logue, R. B and Laws, C. *J Allergy* 13-414-416 (May) 1942
25. Fell, N., Rodney, G and Marshall, D E. *J Immunol.*, 47 237-249 (Sept.) 1943
26. Cohen M B and Friedman H J. *J Allergy* 14 195-202 (March) 1943
27. Sheldon, J M., Fell N., Johnston, J H and Howes, H A. *J Allergy* 13 18-30 (Nov) 1941
28. Ruskin, S L. *Arch Otolaryng.*, 56 853-873 (Dec.) 1942
29. Westcott, F H and Gillson R E. *J Allergy* 14 420-427 (July) 1943
30. Lockey S. D. *J Allergy* 14 382-385 (July) 1943
31. Barach, A L. *J Allergy* 14 296-309 (May) 1943
32. Gay L N and Reinhoff W M. *Bull Johns Hopkins Hosp.*, 70 386-393 (April) 1942
33. Gaarde, F W., Prickman, L. E. and Raszkowski H J. *J.A.M.A.*, 120-431-433 (Oct. 10) 1942
34. Unger L. and Wolf A. A. *J.A.M.A.*, 127 325-330 (Jan. 30) 1943

## THE VENTRICULAR GRADIENT

GEORGE BURCH, MD, FACP\*

THE ventricular gradient had been neglected for several years even though Wilson, MacLeod, Barker and Johnston<sup>1</sup> had indicated the importance of the index. Ashman and his associates<sup>2, 3, 4, 5, 6</sup> and Bayley<sup>2, 7</sup> have recently revived the problem by presenting more practical methods for the analysis and interpretation of the ventricular gradient. Because of the importance of this factor in clinical electrocardiography and the recent interest in the subject, it is considered advisable to summarize the literature with the purpose of presenting in a simplified fashion the concept of the ventricular gradient, although its clinical application will not be reviewed in detail. In order to understand the subject more clearly, certain fundamental aspects of the theory of electrocardiography must be reviewed.

In the process of the activation of living cells, such as muscles, electrical phenomena occur which can be recorded by a sensitive galvanometer. The precise nature of the physicochemical changes associated with these electrical processes is unknown. The theories concerning them are similar, although each observer adheres to certain differences in the presentation of his concepts. In the following discussion Ashman and Hull's<sup>8</sup> method of presentation is employed since it is simple to interpret.

Every living cell has a series of positive charges on the external surface of its wall and negative ones on the internal surface. These are equal in number. Each pair is known as a *doublet*. A living cell surfaced by these doublets is said to be *polarized* (Fig 85, a). If the cell is in a volume conductor, that is, a medium which will conduct electricity in all three directions such as a bath of physiologic sodium chloride solution (the human body is a volume conductor), the electrical phenomena associated with change in the polarized state of the cell can be recorded by a sensitive galvanometer, such as the clinical electrocardiograph. If the electrodes RA (right arm), LA (left arm) and LL (left leg) were placed in the volume conductor (bath of physiologic sodium chloride solution) as indicated in Figure 85 to form the apices of an equilateral triangle around a living "cell" and a stimulus applied at the point indicated by the arrow, the polarized state of the "cell" would be disturbed. The resistance of the cell wall would be lowered locally by the stimulus. The plus and minus charges would

---

From the Division of Medicine, Ochsner Clinic and the Department of Medicine, Tulane University School of Medicine, New Orleans.

\* Associate Professor of Medicine, Tulane University School of Medicine, Consultant in Cardiovascular Diseases, Ochsner Clinic.

then reach each other and be discharged. In so doing the resistance of the adjacent cell wall would be reduced and the adjacent plus and minus charges would also be discharged. This would continue around *ad seriatim* until the entire cell lost its doublets. (The completeness with which the doublets are lost is unknown. It is unlikely that they are lost entirely except possibly with death of the cell. In this discussion, for the purpose of simplicity, it will be assumed that all are lost.) This process of discharging of the plus and minus charges is referred to as *depolarization*, at its completion the cell is said to be *depolarized*.

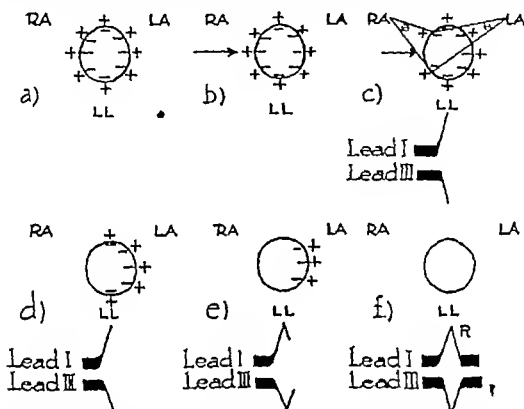


Fig 85—Diagrammatic representation of a polarized living resting cell, and the stages in the change in the polarized state following stimulation at the point indicated by the arrow. The completed galvanometer recording of the electrical force associated with the changes in the state of polarization are also shown. The size of the solid angle subtended by the cell at the electrode will determine the force offered by the cell at that electrode. The charge of the potential offered by the cell at that electrode is determined by the charge first seen, were an observer to peep through a hole in the apex of the solid angle and look at the cell. In *c* the charge of the field about RA is negative and the one at LA is positive (see text for further details).

From Figure 85, *c*, *d*, *e* and *f* it can be seen that as the depolarization of the cell occurs, the RA electrode finds itself in a field of *relative negativity* and the LA electrode in a field of *relative positivity*. The nature of the charge influencing the electrodes is determined in part by the distances of each electrode to the various charges. An analogy may be made with the field around the anode and the cathode in electrolysis, the field near the former is relatively positive and that around the latter relatively negative. From Figure 85 it can be seen that the intensity of the negative and positive potentials in the two fields about

the RA and LA (the electrodes of Lead I) will vary with the extent of the depolarization of the cell (consult Ashman and Hull<sup>8</sup> for details)

If the electrodes are connected to a galvanometer and a photographic record made, there results a tracing representing the electrical activity produced by the *depolarization* of the cell. The recorded complex is known as the *wave of depolarization*. If it is assumed that depolarization occurs uniformly around the surface of the cell, a smooth wave will result (Fig 85). It is also well to remember that the

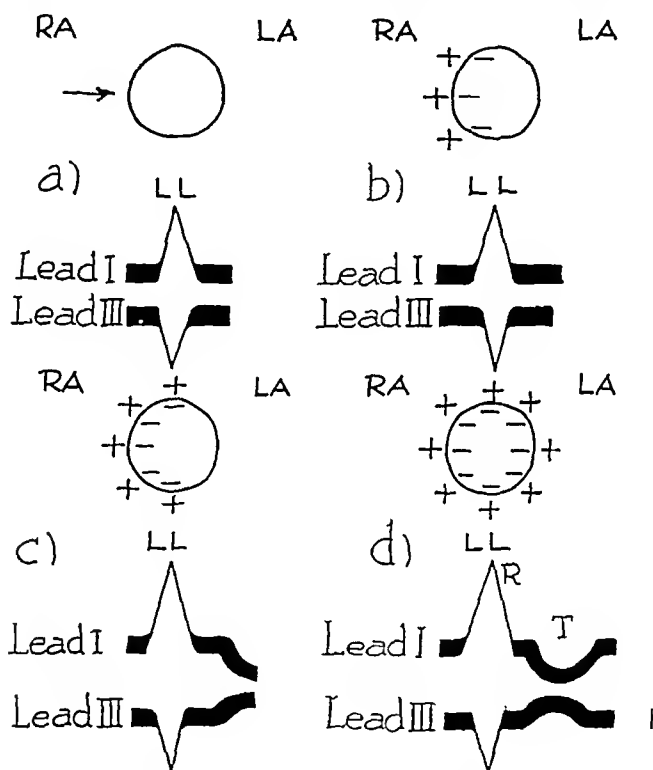


Fig 86—The process of repolarization with the repolarization wave (T) written in the completed recording

galvanometer is so connected that when the RA electrode is in a negative field and the LA in a positive field the galvanometer is deflected upward or in a positive direction. Since the fields are such in Figure 85, the depolarization is positive in Lead I. The galvanometer connections are so made that when the LA and LL electrodes are used to record Lead III, an upright or positive deflection is also recorded whenever the LA electrode is in a field of relative negativity and the LL electrode is in a field of relative positivity. During the depolarization of the cell shown in Figure 85, it can be observed that the LA electrode is in a field that is more positive than the LL electrode and

therefore the galvanometer string is deflected to the negative side recording a negative or downward wave of depolarization

Living depolarized cells are endowed with the ability to restore themselves to the resting state by means of certain physicochemical phenomena aided by enzymes reacting with foodstuffs, oxygen and other substances. This restoration begins almost immediately at the site where depolarization first began. If it takes place in a uniform manner, it will occur around the cell in a fashion similar to that described for depolarization. The restitution of the doublets to the original state is spoken of as *repolarization* (Fig 86). The rate of *depolarization* is more rapid than the rate of *repolarization*, but the intensity of the electrical force attained is greater in the former than in the latter as is indicated by relative amplitudes of the wave of depolarization and repolarization shown in Figures 85 and 86. The repolarization wave is

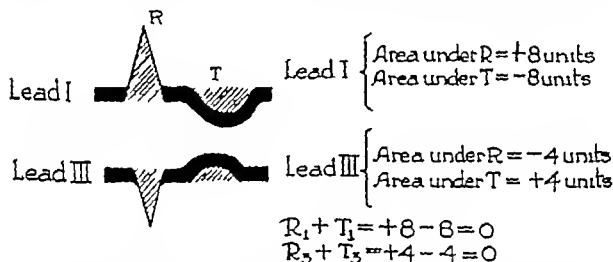


Fig 87.—When the order of depolarization or accession is regular and uniform in rate and all portions of the "cell" remain in the excited state for an equal length of time, the order of repolarization or regression must follow the path of accession and will be regular and uniform and the ventricular gradient will not exist.

negative in Lead I for during repolarization the RA electrode is in a field of relative positivity and the LA electrode is in a field of relative negativity thus reversing the polarity and flow of current in the galvanometer and thereby resulting in a deflection below the *isoelectric* or base line or a negative wave (T wave). In Lead III the LA is in a field of relative negativity during repolarization and the LL electrode is in a field of relative positivity. This results in a positive or upright repolarization wave (T wave) in this lead.

The total force represented by the *depolarization* or *repolarization* waves may be measured by determining the area under each curve. The area under each of these waves is equal in Lead I and Lead III (Figs 86 and 87). One wave is positive and the other negative in each lead (Fig 87).

The depolarization wave is designated the R wave and the repolar-

ization wave the T wave in order to draw an analogy between this *theoretic* spherical cell of muscle and the human heart and the waves of depolarization and repolarization in the human electrocardiogram

When the living cell is in the depolarized state, it is said to be in the *excited* state. When it is in the polarized state, it is said to be in the *resting* state. If following the application of a stimulus every *portion* of the cell remains depolarized or in the excited state for an equal length of time, it means that the area under the R wave must equal that under the T wave and that the order of *repolarization* retraced exactly the order of *depolarization*. This, of course, indicates also that the areas under R and T must be opposite in sign as well as equal. Therefore, if the values of the areas under R and T are added algebraically, the result is zero, this indicates that the duration of the *excited state* is *equal* throughout the cell. Wilson and his associates made use of this addition in order to express the *duration of the excited state* of the ventricular musculature in absolute units. This expression of the duration of the excited state they called the *ventricular gradient*. In summary, then, the ventricular gradient is an expression of the variations in the duration of the excited state. Later it will be seen that it can be represented as a vector force possessing all of the mathematical characteristics of such a force.

It has been indicated in the preceding discussion that when the duration of the excited state is equal throughout in the hypothetical cell, the ventricular gradient is zero (Fig. 87) or there is no gradient. By necessity the order of repolarization has retraced exactly the order of depolarization. Should the duration of the excited state not be uniform throughout, the ventricular gradient will have an absolute value and the direction and magnitude of the vector representing the gradient will be determined by the nature of these variations. For example, in Figure 88, the M half of the cell has been cooled to 15° C, this delays depolarization and the physicochemical processes leading to repolarization so that repolarization begins on the N half first. The duration of the excited state, therefore, is not equal throughout the cell, it is longer in the M half. In the resulting tracing the repolarization wave will also be upright and the gradient will be greater than zero or it possesses an absolute value.

The vector representing the gradient points in a direction from the point in the cell in which the duration of the excited state is longest to that in which it is shortest, in this case from the right of the cell to the left as indicated by the heavy arrow in Figure 88. Obviously, if the N half of the hypothetical cell were cooled, the arrow would point from the left of the cell to the right or if the positions of the electrodes, RA and LA, were exchanged, it would point from the left of the cell to the right. The influence of rotation of the cell will likewise affect the direction. For example, if in Figure 88 the cell had been rotated clockwise through an angle of 180 degrees, the vector representing the

gradient would point from left to right instead of from the right of the cell to the left. Therefore, rotation of the cell or the relationship of electrodes to each other and to the cell will influence the direction, and obviously, the manifest magnitude (defined later) of the gradient.

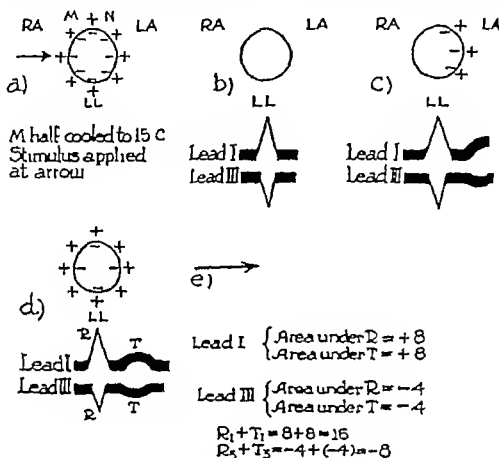


Fig 88—The M half of the cell was cooled to 15 C, thus delaying the physicochemical process in the M half of the cell. When a stimulus is applied to the M half at the point indicated by the arrow, depolarization occurs relatively slowly. When the impulse reaches the N half of the cell, the depolarization process speeds up and progresses in a normal fashion. Since the M half is cooled, the physicochemical process associated with recuperation and repolarization or regression is slowed so that repolarization begins on the N half of the cell (c) thus resulting in an order of regression which is opposite in direction to the order of depolarization or accession. This also results in a pronounced variation in the duration of the excited state for various portions of the cell. In this example the M half remained in the excited state for a much longer period of time than the N half. This also resulted in regression waves (T waves) with areas of the same sign as the areas of the accession waves (R waves). There is a definite gradient. A vector representing the gradient points for the point in which the mean duration of the excited states is longest to the point where the mean duration is shortest. In this example it would point then from the center of the M half of the cell horizontally across to the center of the N half (heavy arrow e).

Again, the vector force expressing the depolarization (R) and repolarization (T) may be correlated independently with the gradient as well as with each other.

Wilson, Bayley, Ashman and their co-workers have applied the same reasoning to the human heart. By determining the area under the de-



polarization complex (QRS) and repolarization complex (T) of the human electrocardiogram and adding these areas algebraically the *ventricular gradient* is determined. It has the same significance as for the hypothetical cell (previously described). It is a vector expression (in quantitative terms), of the relative variations in duration of the excited state in the different portions of the ventricular musculature. It is an expression of the relationship of the orders of depolarization and repolarization. The vector representing the gradient points from the area in the heart in which the average duration of the excited state is longest to that where it is shortest. In the normal human heart the direction is from endocardial surface to epicardial surface and the angle it forms with the horizontal or Lead I line is normally close to that of the QRS complex and close to the longitudinal anatomic axis of the heart.

#### NOMENCLATURE

From the preceding discussion it is obvious that not only is the ventricular gradient a vector force but so is the electrical axis of the P, QRS and T waves. The anatomic axis (the longitudinal axis of the heart drawn from the base of the heart to the apex) obviously is not a vector force as it possesses only the quality of direction. Bayley<sup>2</sup> has suggested a type of nomenclature and symbols to represent these forces in order to simplify discussions (Fig 89). The symbols and their connotations are as follows:

$G$  = Ventricular gradient as projected on the frontal plane of the body

$A_{QRS}$  = Mean manifest magnitude of the QRS complex determined algebraically and measured in microvolt seconds or units, i.e. the mean force of the depolarization process of the ventricular musculature

$H$  = Anatomic (longitudinal) axis of the heart as projected on the frontal plane. This value has no magnitude and cannot be expressed quantitatively

$A_T$  = Mean manifest magnitude of the repolarization process in microvolt seconds or units

When the arrow tip or caret ( $\wedge$ ) is placed over the symbols as follows,  $\hat{A}_{QRS}$ ,  $\hat{G}$  or  $\hat{A}_T$ , it indicates that the particular value is to be considered as a *vector*, i.e., it has direction, magnitude and sense. The direction is expressed in degrees according to the old concepts of Einthoven (Bayley suggested the use of the polar coordinate system of measurement, a more correct form mathematically, but because of general practice and until a new method is generally agreed upon it is probably better to adhere to the old empirical method of expressing the direction of the vector forces in order to avoid confusion), i.e., as the angle in degrees the vector forms with the zero or horizontal or Lead I line (Fig 89,  $\alpha$ ).

It is known that when the three standard leads are used, the electrical forces of the heart projected on the frontal plane of the body (the manifest forces) are the ones recorded. Actually, however, these forces are extended into space away from the frontal plane.<sup>1 2 3</sup> For example, the H axis projects anteriorly down and to the left, the  $\bar{G}$  also points down, to the left and only slightly anteriorly, while the  $A_{QRS}$  points down to the left and slightly posteriorly (Fig 89, b). In order to represent the spatial vector Bayley<sup>2</sup> suggested the prefix S be used as fol-

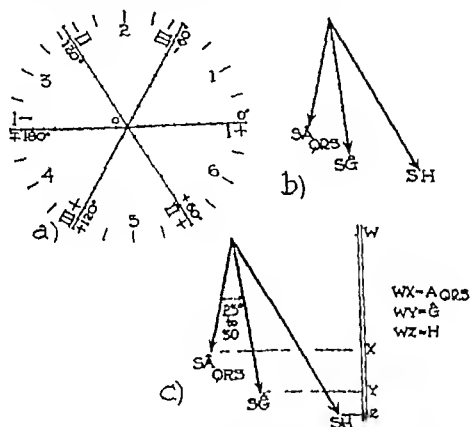


Fig 89—*a*, Triaxial reference system suggested by Bayley<sup>2</sup> for the analysis of the forces concerned with the electrocardiogram *b*, The spatial vector forces of the QRS ( $A_{QRS}$ ) and gradient ( $\bar{G}$ ) and the longitudinal anatomic axis of the heart (H) *c*, In the analysis of the standard or limb leads of the electrocardiogram only that portion of the spatial forces projected upon the frontal plane of the body is recorded. These values are called *manifest* values. For example, WX, simply called  $A_{QRS}$ , is the *manifest vector* force of the spatial vector  $SA_{QRS}$ , WY simply called  $\bar{G}$  is the *manifest vector* force of the spatial vector SG and WZ, simply called H, is the *manifest longitudinal anatomic axis* of the spatial axis SH.

lows  $SA_{QRS}$ ,  $SA_T$  or SG. For example,  $\bar{G}$  would represent only that portion of the spatial ventricular gradient that is projected on the frontal plane whereas SG would represent the entire ventricular gradient as a vector force extended into space, i.e., the spatial gradient. From Figure 89 it can be seen that SG has a greater magnitude than  $\bar{G}$ , the latter being represented by the projected magnitude WY. Furthermore, SG has three directions. In the normal person it is directed (1) down, (2) to the left and (3) anteriorly, whereas  $\bar{G}$  has only two

directions—(1) down and (2) to the left, i.e., it is considered only in one plane, along the frontal plane of the body. The spatial values are of very little use in clinical electrocardiography today but are valuable in the appreciation of the fundamental forces concerned. In fact, it is a necessary concept for detailed understanding of the nature of the forces involved. The spatial force projected on the frontal plane is known as the *manifest* force. It is the force manifested by the completed electrocardiogram.

#### METHOD OF MEASUREMENT AND RECORDING

Ashman and his associates<sup>2</sup> have simplified the method of measuring the ventricular gradient to make it practical and still accurate enough to have clinical applications. They suggested the following procedure. The areas of the QRS and T (the depolarization and repolarization complexes) are determined as shown graphically in Figure 90. The

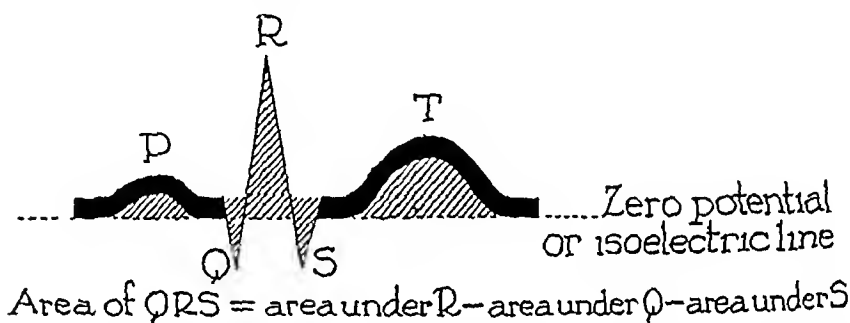


Fig 90—Diagram showing the areas measured to determine the area under the QRS complex and the area under the T wave. Areas above the isoelectric line are considered to be positive values and those below the isoelectric line are negative.

areas above the isoelectric line are positive values and those below negative. The areas are determined by counting the "squares" formed by the millimeter and time lines or the areas may be determined by measuring the height of a complex in microvolts (1 millimeter is equal to 100 microvolts in a properly standardized electrocardiogram) and multiplying this factor by one-half the width of the base in seconds. A lens for magnification aids in these measurements. The units are expressed in microvolt seconds. Since each time line is 0.04 second apart and each millimeter line represents 100 microvolts with the usual standardization, then each small rectangular division on the tracing represents 4 (often referred to as *one unit*) microvolt seconds (m.v.s.). The algebraic addition of the positive and negative values is equal to the net area of the QRS and T or net magnitude of the depolarization and repolarization processes respectively.

In order to find  $\bar{G}$ , one finds  $\bar{A}_{QRS}$  and  $\bar{A}_T$  from any two leads, preferably Leads I and III, by obtaining the algebraic sum of the areas of

QRS and T for the two leads and adding them as vector quantities. For example, suppose the net area of the QRS in Lead I is plus 2 and in Lead III plus 6 and the net area of T in Lead I is plus 3 and in Lead III plus 0.5, then  $\hat{G}$  would be as indicated in Figure 91

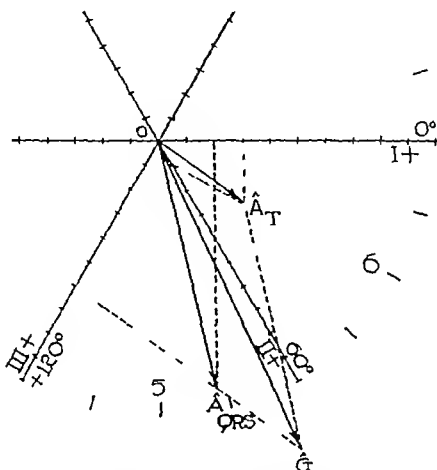


Fig 91—Method of finding the gradient,  $\hat{G}$ , from the following values: QRS in Lead I  $\approx +2$  units, QRS in Lead III  $\approx +6$  units, T in Lead I  $\approx +3$  units, T in Lead III  $\approx +0.5$  units.  $\hat{G}$  has a magnitude of 12.5 units and a direction of  $+65^\circ$ .  $A_{QRS}$  and  $A_T$  were first found as described in the text. Then  $\hat{G}$  was found by means of the parallelogram law of analysis of vector forces.

More cumbersome methods have been employed to increase the accuracy of the measurements (1) but Ashman and his associates<sup>3</sup> have found the method described to be accurate to  $\pm 15$  per cent for the magnitude and  $\pm 5$  degrees for the direction of  $\hat{G}$ .

#### FACTORS INFLUENCING THE VENTRICULAR GRADIENT

Certain factors will influence the direction and magnitude of the ventricular gradient. These factors are important in health and in disease. Some of the known factors are included below.<sup>1 2 3 4 5 6 7</sup>

*Rotation of the heart about its anteroposterior axis* will change the ventricular gradient.<sup>2</sup> Rotation *counterclockwise* (rotation to the left) will rotate the axis of  $\hat{G}$  to the left and make it transverse. The axis of  $\hat{G}$  is rotated more than the anatomic axis of the heart. A rotation to the right, or *clockwise* rotation, will make  $\hat{G}$  vertical, i.e.,  $\hat{G}$  will rotate

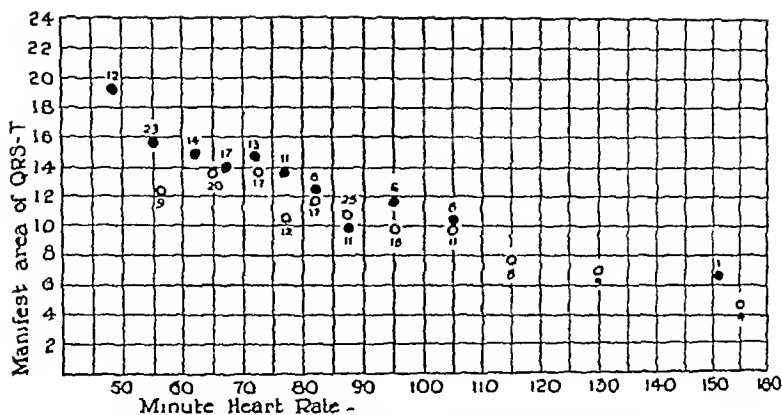
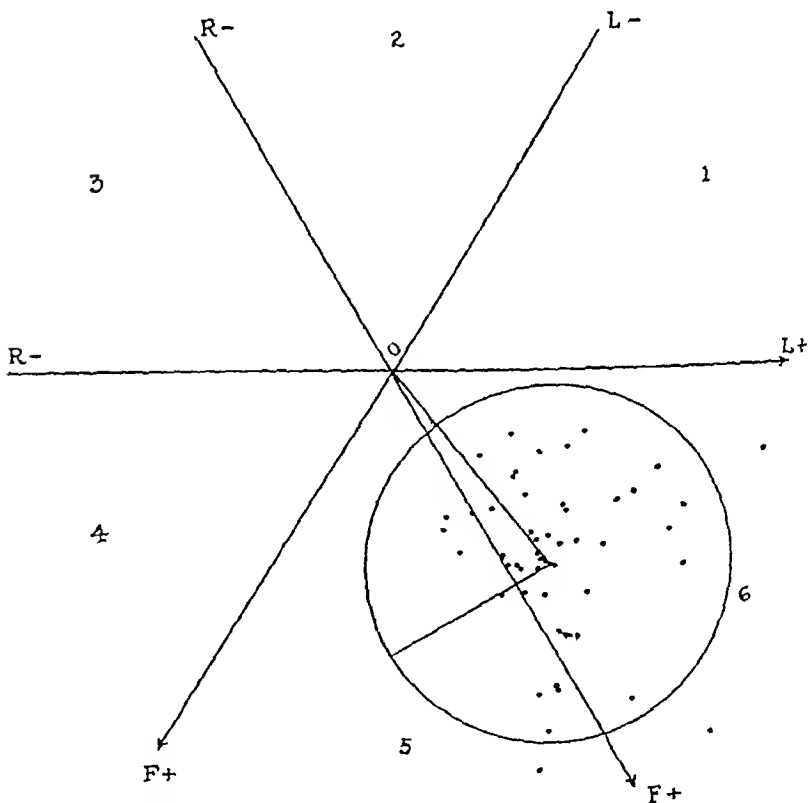


Fig 92 -Correlation of heart rate and the gradient.<sup>8</sup> The numbers near each dot or circle indicate the number of subjects studied

Deviation of  $A_{QRS}$  with respect to  
the normal ventricular gradient

Max  $+L = 24^\circ$ , Mag=11.48 mvs

Max  $-L = -35^\circ$ , Mag=10.80 mvs



A circle of radius 42 mvs  
centered 58 mvs from the  
origin at an  $\angle$  of  $-50^\circ$  includes  
95% of termini of norm grads

Fig 93 -Gradients of 100 normal adults The dots indicate the termini of the gradients"

to the right. The range of normal rotation of  $\bar{G}$  is greater than that of the anatomic axis (H), but not as great as that of  $A_{QRS}$ .

*Rotation of the heart about its longitudinal axis* will change the ventricular gradient.<sup>2</sup> From Figures 89, c and 94 it is obvious that rotation of the heart about the H axis (longitudinal anatomic axis) will change the relationship of the axis of  $\bar{G}$ , QRS and H. Bayley, Holoubeck and Baker, quoted by Ashman,<sup>2</sup> have shown that in normal subjects the axis of the gradient should not be more than 24 degrees to the right of the QRS axis and not more than 35 degrees to the left of it.

The influence of *rotation of the heart about its transverse axis* upon the gradient is not well known.<sup>2</sup>

*Posture*, by its influence, in a large part at least on cardiac position, will change the gradient.<sup>2</sup> Standing decreases the magnitude of the gradient and tends to rotate it to the right.

*Heart rate* will change the magnitude and direction of the gradient<sup>2</sup> (Fig 92). An increase in rate will tend to decrease the magnitude of the manifest area of the gradient.<sup>2</sup> These changes are probably related to many changes associated with the causes for the increase in pulse rate.<sup>2</sup>

The normal variations of gradient are shown in Figure 93 taken from the work of Bayley.<sup>7</sup>

#### RELATIONSHIP OF THE VENTRICULAR GRADIENT TO THE QRS AXIS AND THE LONGITUDINAL ANATOMIC AXIS OF THE HEART

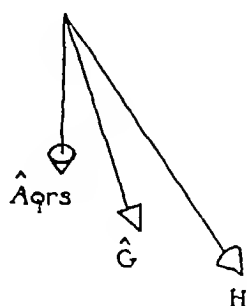
Ashman and Byer<sup>2</sup> studied the relation of the manifest magnitudes of the axis of the gradient and QRS axis and like Bayley<sup>7</sup> found the two to be closely related in the normal subject. This relationship is shown in Figure 94. The two axes tend to follow each other rather closely and fall more or less within the range previously quoted from the studies of Bayley.<sup>7</sup> From a careful study of Figure 94 it can be seen that the spatial arrangement of the QRS and  $\bar{G}$  axes about the anatomic axis (H) are such that rotation of the heart along the longitudinal anatomic axis in a counterclockwise direction (when looking at the apex of the heart) will rotate the  $\bar{G}$  axis to the left of H and to the right of the QRS axis. Rotation of the heart in a clockwise direction along the longitudinal anatomic axis will rotate the  $\bar{G}$  axis to the right of the H axis and the QRS axis to the right of the  $\bar{G}$  axis.

#### NORMAL VALUES OF THE GRADIENT

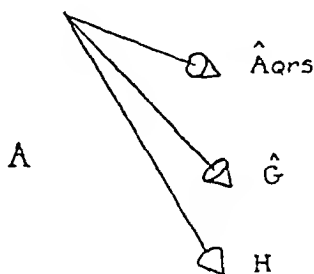
The manifest magnitude of the  $\bar{G}$  averages 13 units (1 unit is equal to 4 microvolt seconds). The magnitude is slightly greater in men than in women. The mean manifest magnitude of  $A_{QRS}$  is 5.9 units in women and 6.7 units in men, i.e.,  $\bar{G}$  is about double  $A_{QRS}$ . A 50 per cent increase in heart rate decreases the  $\bar{G}$  about 39 per cent in magnitude. The maximum magnitude of  $\bar{G}$  is probably not known, but

normally it is near 23 units and the minimum is about 2.5 units. The maximum magnitude of  $\hat{A}_{QRS}$  is about 12 units and the minimum about minus 3.5 units.

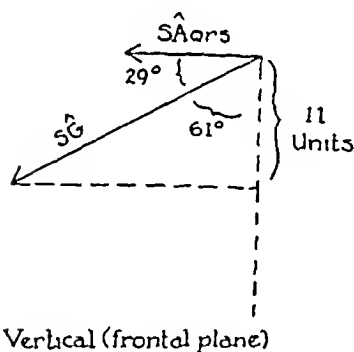
$\hat{G}$  normally forms an angle of plus 20 degrees or less with the longitudinal anatomic axis (H).  $\hat{G}$  rarely is found normally outside of 0 and plus 90 degrees, i.e., it is rarely outside the sixth and adjacent half



Slight clockwise rotation about H

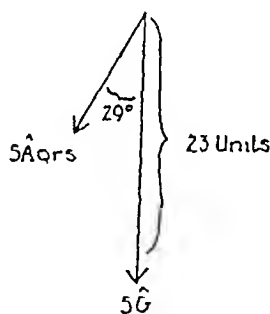


Slight counter clockwise rotation about H



Vertical (frontal plane)

B



C

Fig 94—Correlation of the spatial and manifest axes of the  $\hat{A}_{QRS}$ ,  $\hat{G}$  and  $H$  axes as influenced by rotation of the heart. B, The spatial axes as seen in a right lateral view when the axes lie in a sagittal plane. The vertical dotted line marks the intersection of frontal and sagittal planes. C, The spatial electrical axes after rotation of the heart so that  $S\hat{G}$  marks the intersection of frontal and sagittal planes.

of the fifth sextants of the triaxial reference system (Fig 89, a). As previously mentioned  $\hat{G}$  normally lies not over 24 degrees to the right of  $\hat{A}_{QRS}$  and 35 degrees to the left of  $\hat{A}_{QRS}$ .

Bayley<sup>7</sup> has stated that if the terminus of  $\hat{A}_{QRS}$  describes an arbitrary path about 0, the center, in the triaxial reference system while  $\hat{G}$  remains fixed, the terminus of  $\hat{A}_T$  describes a similar path (appearing as if rotated through 180 degrees) about the terminus of  $\hat{G}$ . The path of

$\bar{A}_T$  thus describes all possible variations of  $\bar{A}_{QRS}$ . If the terminus of  $\bar{G}$  is made to describe an arbitrary path about 0 while  $\bar{A}_{QRS}$  remains fixed, the terminus of  $\bar{A}_T$  describes a similar path about the terminus of minus  $\bar{A}_{QRS}$ . The path of  $\bar{A}_T$  describes any variations in  $\bar{A}_T$  due to all possible variations in  $\bar{G}$ . These rules make it possible to distinguish primary T wave changes from secondary T wave changes, an important differentiation.

Drugs, fainting and the like<sup>3</sup> have been studied. A discussion of their effects is beyond the scope of this presentation.

#### CLINICAL APPLICATION OF THE VENTRICULAR GRADIENT

In disease the ventricular gradient is changed in magnitude and direction as well as in its relationship to the axis of the QRS and the anatomic axis (H). For example, it is possible to interpret the significance of the T wave changes in the electrocardiogram with the use of the gradient. T wave changes secondary to changes in the position of the heart will possess a normal gradient in all respects, whereas if primary T wave changes occur as a result of diseases of the myocardium, the gradient will be abnormal in its magnitude, direction or relation to the other axes. At times all three changes are present simultaneously.<sup>3, 7</sup> For example, coronary occlusion which produces primary T wave changes will characteristically alter the gradient. In strictly apical myocardial infarction the gradient is shorter or even reversed and located in the third sextant,<sup>7</sup> whereas a diffuse basal infarction will produce a gradient of excessive magnitude.<sup>7</sup> In general ischemia of the heart due to impairment of the circulation through the right coronary artery will produce rotation of  $\bar{G}$  to the left or within the first or second sextant whereas ischemia of that portion of the heart supplied by the left coronary artery will rotate  $\bar{G}$  to the right or into the fifth sextant.

When there is doubt about many changes in the electrocardiogram such as low or negative T waves in Lead I in clinically normal persons, the gradient is of paramount assistance in determining the clinical significance of such T waves.

If there is a greater than normal deviation in the angles between the  $\bar{A}_{QRS}$  and  $\bar{G}$  and H axes than would be expected on rotation of the heart alone, it is safe to conclude that there is disease of the myocardium. Such questions frequently arise in subjects with vertical or transverse hearts in whom changes produced by rotation and disease are difficult to differentiate.

It is impossible in a paper such as this to review in detail the explanations for changes in the gradient with each type of disease. With a knowledge of the fundamental concept of the gradient it is possible to arrive at such explanations. A consultation of the works of Wilson, Ashman and Bayley and their associates will assist the reader in these interpretations.



## SUMMARY

The literature concerning the ventricular gradient is reviewed. The concept is presented in simple form in order to acquaint the reader with the nature of the problem and the underlying ideas involved. The nomenclature, normal values, some of the normal correlations with the electrical axes of the QRS complex and T wave and the longitudinal anatomic axis are presented. The general clinical applications of the ventricular gradient are indicated, but not reviewed in detail.

## BIBLIOGRAPHY

- 1 Wilson, F. N., MacLeod, A. G., Barker, P. S. and Johnston, F. D. *Am Heart J.*, 10 46-61 (Oct) 1934
- 2 Ashman, R., Byer, E. and Bayley, R. H. *Am Heart J.*, 25 16-35 (Jan) 1943
- 3 Ashman, R. and Byer, E. *Am Heart J.*, 25 36-57 (Jan) 1943
- 4 Ashman, R., Gardberg, M. and Byer, E. *Am Heart J.*, 26 473-494 (Oct) 1943
- 5 Ashman, R. *Am Heart J.*, 26 495-510 (Oct) 1943
- 6 Gardberg, M. and Ashman, R. *Arch Int. Med.*, 72 210-230 (Aug) 1943
- 7 Bayley, R. H. *Am Heart J.*, 26 769-831 (Dec) 1943
- 8 Ashman, R. and Hull, E. *Essentials of Electrocardiography*, ed 2 New York, The Macmillan Co., 1941

# RECENT ADVANCES IN THE THERAPY OF CIRRHOSIS OF THE LIVER

LEO J. WADE, M.D.\*

CIRRHOSIS of the liver is characterized anatomically by (1) fatty infiltration and necrosis of liver cells, (2) regeneration of liver cells and bile ducts, and (3) a relative increase in fibrous tissue. Clinically, an insidious onset is followed by one or more of the following three acute manifestations (1) gastrointestinal hemorrhage, (2) jaundice and (3) ascites.

## PATHOGENESIS AND ETIOLOGY

On the basis of clinical, anatomical and experimental observations one may conclude that fatty infiltration of hepatic cells is sometimes followed by necrosis of these cells with subsequent proliferation of fibrous tissue and attempted regeneration of liver cells and bile ducts.<sup>6</sup> Any agents or factors which are capable of bringing about fatty infiltration of the hepatic cell if sufficiently prolonged might reasonably be expected to produce cirrhosis. It is probable, therefore, that multiple etiologic agents may produce the disease.

*Alcohol* is probably not a primary etiologic agent. Cirrhosis cannot be produced experimentally by alcohol ingestion alone and cirrhosis may occur in the absence of excessive alcohol consumption. A common factor among the alcoholic population which is probably of great etiologic importance is *malnutrition*. The dietary habits of the chronic alcoholic are notoriously bad, the diet being inadequate in both quality and quantity of many essential food factors, particularly proteins and the vitamin B complex. Cirrhosis can be produced in the experimental animal by deprivation of certain amino acids and vitamins.<sup>12, 21, 22</sup> Therapeutic results obtained in human cases by attempting to correct nutritional disorders suggested by these concepts has led many observers to the belief that nutritional factors are responsible for most cases of cirrhosis seen in this country.<sup>3, 4, 8, 10, 16</sup>

## INCIDENCE

Over a ten-year period we have accumulated 175 autopsied cases of cirrhosis of the liver in an autopsy series of approximately 8000 cases.

From the Department of Medicine and the Snodgrass Laboratories of the St. Louis City Hospital, and the Department of Medicine of the Washington University School of Medicine St. Louis, Missouri.

Medical Director of the St. Louis City Hospital. Instructor in Medicine, Washington University School of Medicine. Assistant Physician, Barnes Hospital. Consulting Physician, Missouri Pacific Hospital.

This represents an incidence of 2.2 per cent.\* The corrected sex incidence is three males to every two females. The majority of the male patients were in the sixth decade while most of the female patients were in their fifth decade. The patient with advanced disease was on the average five to ten years younger than the patient in whom cirrhosis was an incidental and often an unexpected autopsy finding.

Bartenders, liquor dealers and brewery workers were found among the cirrhotic patients about 50 times as often as among the entire hospital population. Mechanics, electricians, painters, salesmen, time-keepers and watchmen were six to seven times as frequent in the cirrhotic group. Factory workers were about one-fourth as common among patients with cirrhosis.

### DIAGNOSIS

As will be emphasized later, success in therapy is dependent upon the early recognition of the disease. Unfortunately cirrhosis is rarely suspected prior to the onset of jaundice, ascites or hemorrhage. The prognosis is grave after the appearance of any one of these three signs or symptoms, 50 per cent of such individuals die within six months<sup>19</sup>. It behooves the physician, therefore, to suspect cirrhosis, as he does cancer, before the classical textbook picture appears.

**Symptoms**—The earliest manifestations of the disease are insidious in onset. *Periodic bouts of digestive disturbances* characterized by anorexia, morning nausea and vomiting, gaseous distention and irregularity of the bowels are common (73 per cent). If these are accompanied by a history of an inadequate diet, chronic alcoholism and an enlarged liver, the diagnosis of cirrhosis should be strongly suspected and therapy instituted unless the above signs and symptoms can be adequately explained on the basis of other demonstrable disease processes.

*Weakness and loss of weight* follow these earliest manifestations in 95 per cent of the patients. In contrast with the digestive disturbances which may persist for months or even years, weakness and loss of weight are rapidly progressive. Ascites, jaundice and/or gastric hemorrhage soon appear.

*Ascites* occurs in about 65 per cent of the patients. It is four or five times as common in advanced cases as it is in those with early or minimal lesions. The fluid is a transudate and its formation is dependent upon two factors: (1) a decrease in the serum albumin (below  $3.1 \pm 0.2$  gm per 100 cc<sup>18</sup>) and (2) an increase in the venous pressure in the portal system. The decreased serum albumin is the result of

\* Reference will be made throughout this paper to the clinical and anatomical findings in 175 autopsied cases of cirrhosis of the liver studied at the St. Louis City Hospital. The author wishes to express his sincere thanks to Lt. Wm I Park, Jr (formerly Assistant Resident in Pathology) for his invaluable aid in the collection of these data.

inadequate protein intake, inadequate absorption and impairment of the liver's ability to synthesize albumin. The increased portal pressure is probably the result of back pressure from the arterial system due to abnormal communications between the branches of the portal vein and the hepatic artery.<sup>13</sup>

*Ankle and scrotal edema* may precede, accompany or follow the ascites. Decrease in the serum albumin is the precipitating factor in most instances, but pressure on the iliac veins by large accumulations of ascitic fluid may be contributory. Change in the intensity of this latter factor with changes in position may be responsible for nocturnal variations in the ankle edema in some instances.

*Hematemesis* may be expected in about 70 per cent of the cases. It too is far more common in the advanced case (six or seven times) than

TABLE 1—CHIEF SYMPTOMS NOTED AMONG 175 CASES OF CIRRHOSIS OF THE LIVER PROVED AT AUTOPSY\*

Symptoms	Grade 1	Grade 2	Grade 3	Average
	Per Cent	Per Cent	Per Cent	Per Cent
Anorexia	50 0	69 2	79 6	73 0
Loss of weight	66 7	53 2	70 0	64 0
Weakness	83 3	88 2	100 0	93 8
Ascites	17 7	54 8	79 2	62 6
Ankle edema	40 0	58 2	74 2	64 2
Hematemesis	12 5	31 5	67 8	54 7
Jaundice	11 1	30 3	81 2	48 2

\* Grades 1, 2 and 3 indicate increasing amounts of liver destruction and fibrosis.

in early cirrhosis. Such hemorrhages are probably secondary to rupture of an esophageal varix in most instances although considerable bleeding may result from prothrombin and vitamin deficiencies.

*Jaundice* is present at some time or other during the course of the disease in 80 per cent of the patients. It is usually not intense and may be of brief duration. Both obstructive and hepatogenous factors are responsible for the bile pigment retention. (See Table 1.)

**Physical Signs.**—A palpable liver may be the only sign elicited on physical examination of the early case. In some instances evidences of multiple vitamin deficiencies are present as well as other indications of malnutrition.

The more advanced case presents a striking picture which can readily be recognized by any sophomore medical student. The sunken cheeks, pinched features, atrophic musculature and muddy complexion (bile pigment retention plus anemia) are in sharp contrast with the large protuberant abdomen usually considered an indication of excess food ingestion. Dilated vascular channels about the nose and occasional

spider hemangiomas on the face, neck and arms may be demonstrated in about half the cases. Pectoral alopecia, scanty axillary hair, a straight pubic hair line and testicular atrophy are common in the male patient. Erythema of the thenar and hypothenar eminences of the hand (liver palm) is present in one third of the cases. The breath sometimes has a "sweetish" odor variously referred to as "new mown hay" or "cow's breath" if liver insufficiency is advanced.

More detailed examination will reveal the diaphragm to be high and to move very little in the presence of ascites. Hydrothorax occurs in 10 to 15 per cent of the cases, such effusions are rarely massive but are easily detectable on physical examination.

TABLE 2 —PHYSICAL FINDINGS NOTED AMONG 175 CASES OF CIRRHOSIS OF THE LIVER PROVED AT AUTOPSY\*

Sign	Grade 1	Grade 2	Grade 3	Average
	Per Cent	Per Cent	Per Cent	Per Cent
Ankle edema	40 0	73 0	70 8	67 6
Ascites	22 2	61 4	79 4	65 8
Dilated veins over abdomen		50 0	72 7	60 0
Emaciation	28 6	34 8	32 9	32 9
Fever	90 3	82 9	63 7	74 4
Hemorrhoids	12 5	26 7	44 5	34 0
Hydrothorax	7 4	16 7	14 7	14 3
Jaundice	7 4	13 3	52 7	32 5
Palmar erythema†				33 3
Pectoral alopecia (males)†				87 5
Spider hemangiomas†				43 3

\* Grades 1, 2 and 3 indicate increasing amounts of liver destruction and fibrosis.

† Observations in thirty consecutive cases of cirrhosis admitted to hospital in past six months.

The skin of the abdomen appears thin and shiny and is traversed by prominent venous channels. A true caput medusae is infrequent. Shifting dullness, a fluid wave and bulging flanks give evidence of the ascites. Removal of this fluid will permit palpation of the liver in most instances (the average weight at autopsy was over 1600 gm). The spleen is usually not palpable unless some antecedent illness or disease is responsible (average weight 333 gm). Edema of the scrotum and ankles is usually associated with massive ascites. Hemorrhoids are described in about one third of the cases. (See Table 2.)

**Laboratory Data**—Several simple laboratory observations are of invaluable help in making the diagnosis of cirrhosis. Anemia is present in 95 per cent of the cases. It is usually not severe, the average count being about 3.5 million per cubic mm. Two types of anemia are seen: (1) a macrocytic anemia similar to Addisonian anemia due to interference with the production and storage of the erythrocyte-maturing

factor, and (2) a hypochromic microcytic type of anemia due to blood loss. The former type is about twice as common as the latter.<sup>11</sup>

*Decrease in serum albumin* occurs in about 95 per cent of these patients. Usually a compensatory increase in the globulin fraction results in a fairly normal total protein and a reversal of the albumin globulin ratio. The serum albumin level is of considerable prognostic value.<sup>18</sup>

Numerous *liver function tests* have been recommended. Two are of value in the diagnosis of cirrhosis.<sup>20</sup> The cephalin-cholesterol flocculation test is positive in about 98 per cent of the cases. Matcer's modification of the Rosenthal bromsulfalein test is also positive in a high percentage of cases. In the presence of jaundice the latter test is of no value.

Anemia, low serum albumin and a positive cephalin-cholesterol test form a triad which gives great weight to a clinical suspicion of cirrhosis.

**Differential Diagnosis.**—A word of caution is necessary to remind the clinician that cirrhosis can be confused with a number of diseases. The following are to be considered: alcoholic gastritis, fatty liver of diabetes or pellagra, von Gierke's disease, leukemia, chronic peritonitis due to the tubercle bacillus, metastases to the peritoneum and the liver, chronic constrictive pericarditis, and Pick's disease. The latter two may masquerade under the guise of cirrhosis for many years. Indeed, the duration of the illness has called our attention to three such cases in the past year.

#### TREATMENT

Intelligent therapy is dependent upon an understanding of the etiology and pathogenesis of disease. If cirrhosis, as has been postulated, is primarily a nutritional disease characterized by fat deposition in the liver which leads to changes in function and structure of that organ, then considerable information is available upon which to base treatment.

Shortly after the discovery of insulin it was noted that insulin did not adequately compensate for the removal of the pancreas of the dog for fatty livers and death ensued unless pancreatic tissue was included in the animal's diet.<sup>1, 9</sup> These observations gave impetus to the accumulation of a mass of experimental data which at present cannot be said to permit any clear-cut conclusions. In short, however, it appears that certain dietary factors (and possibly an internal secretion) exert a *lipotropic effect* and are essential if absorbed fat is to be transported through the liver to peripheral depots. The absence of, or insufficiency of, these factors permits the accumulation of lipids in the liver and results in a secondary fall of the serum lipids.

With these facts in mind it is reasonable to expect that an early or only moderately advanced case of cirrhosis could be arrested by the mobilization of the fat already deposited in the liver and the preven-

tion of any further fat deposition. Accordingly, the following general therapeutic measures are indicated: (1) elimination of any etiologic agent, direct or indirect, such as alcohol and industrial poisons, (2) reduction in the amount of dietary fat available to the liver, (3) assistance in the mobilization of liver fat by the use of lipotropic factors, (4) provision of a diet adequate in all known dietary essentials. The therapeutic regimen used is much the same as that described by Brown and his associates<sup>3, 4</sup> (See Table 3). Each of these measures will be discussed in turn.

1. If the patient suffers from chronic alcoholism one is faced with a very difficult therapeutic problem. There is probably no great harm in the continued ingestion of moderate amounts of alcohol provided the diet and medications are continued. Usually, however, the two are not compatible. The cooperation of the patient's family, a medical social worker and a psychiatrist are invaluable. It has been necessary on more than one occasion to "rescue" patients from local taverns and admit

TABLE 3—THERAPEUTIC REGIMEN

1	No alcoholic beverages	
2	Choline chloride, 1 to 2 gm. daily	
3	Skimmed milk, 1 quart daily	
4	Vitamin A	10,000 U S P units daily*
	B <sub>1</sub>	2-3 mg daily*
	B <sub>2</sub>	3-4 mg daily*
	Niacin	20-30 mg daily*
	C	50-60 mg daily*
	D	800 U S P units daily*
5	Diet	
	Vegetable fat	50 gm daily
	Protein	90-100 gm daily
	Carbohydrate	Sufficient daily

\* Most pharmaceutical concerns dispense vitamin pills or capsules which, in doses of 1 or 2 daily, will adequately fulfill these needs.

them to the hospital in order to prevent interruption of the therapeutic regimen.

2. It is not possible to eliminate all fat from the diet. Such a diet is not practicable and would certainly not be palatable. One can, however, substitute vegetable fat for animal fat thus rendering the diet more palatable and yet markedly reducing the amount of fat carried to the liver. The fat-soluble vitamins must be supplied in another manner. Vitamin A and D concentrates or capsules may be used in quantities sufficient to furnish approximately 10,000 U S P units of A and 800 to 1000 units of D.

3. *Choline* and *methionine* have been used as lipotropic substances. It is thought that methionine is a choline precursor, but the exact mode of action of either substance is unknown.<sup>2</sup> Adequate information upon which to base dosage is not available. Animal experiments indicate, however, that much larger amounts are required to mobilize liver fat than are needed to prevent such fat deposition.<sup>14</sup> The usual dosage of

choline is 1-gm—daily in three divided doses\* It has been possible, however, to give 2 gm daily without any untoward effects in some patients, while others encounter discomfort due to muscarine-like effect (cardiac slowing, increased intestinal movements, and increase of lacrimal salivary and other secretions)<sup>7</sup> Some experimentation with dosage is necessary with each patient starting, of course, with the smaller dose.

Methionine is costly and not readily available. Adequate quantities are present in milk which also affords a good source of other amino acids as well as minerals. Whole milk should not be used because of its butter-fat content. Patients soon learn to enjoy skimmed milk, however, and may request more than the prescribed quart per day.

TABLE 4—SAMPLE DIET

<i>Morning</i>			
Orange juice.	1 cup	Skimmed milk	1½ cups
Cooked oatmeal.	1 cup	Jelly	1 tablespoonful
Whole wheat toast.	2 slices	Oleomargarine*	1 tablespoonful
Coffee or tea	ad lib	Sugar	ad lib
Salt (if no edema)		ad lib	
<i>Noon</i>			
Oysters or fresh cod†	½ cup	Whole wheat bread	2 slices
Potatoes	½ cup	Skimmed milk	1 cup
Vegetables‡	ad lib	Oleomargarine	1½ tablespoonfuls
Salt and sugar	as above	Graham cracker	1
Jelly	1 tablespoonful	Canned pears, apricots, or grapefruit	½ cup
Coffee or tea.	ad lib		
<i>Evening</i>			
Cottage cheese	3 tablespoonfuls	Oleomargarine	2 tablespoonfuls
Vegetables‡	ad lib	Skimmed milk	1 cup
Whole wheat bread.	2 slices	Jelly	2 tablespoonfuls
Pineapple	3 slices	Salt and sugar	as above
Coffee or tea		ad lib	
<i>Bedtime</i>			
Skimmed milk	1 cup	Cookies§	1 or 2

\* Select a brand containing only vegetable oils. Olive oil may be substituted in equal quantities.

† Lean meat, or liver, may be substituted.

‡ Avoid cabbage, corn, cucumbers, lettuce, onions and turnips, which are 'gas formers.'

§ To be made with oleomargarine.

4 Close supervision of the patient's food is essential from the onset. Anorexia will interfere with the ingestion of the prescribed diet unless the patient can be impressed with the great importance of eating. As choline mobilizes the liver fat, the appetite improves and one need

\* A convenient prescription is as follows

Choline chloride	70	0
Syr wild cherry q.s. ad	240	0
Sig Teaspoonful three times daily		



only guide the patient in his choice of food stuffs. The diet (Table 4) should contain

Vegetable fat	50 gm
Protein	90-100 gm
Carbohydrate sufficient for caloric need	

In order to evaluate choline therapy properly, no attempt has been made in this clinic to increase the vitamin B or C content above the accepted adequate daily intake, for Patek has claimed that the vitamin B complex alone will bring about remissions or cures among cirrhotic patients<sup>15, 16, 17</sup>. It is recommended, however, that the vitamin B intake be augmented by the use of yeast or concentrates until such time as the patient's appetite has become sufficiently good to assure adequate dietary sources (See Table 4)

### RESULTS OF THERAPY

Enthusiasm for any sort of therapy of cirrhosis must be tempered by a realization that spontaneous remissions sometimes occur. One must not be easily discouraged, however, by failure to produce improvement in the moribund patient. Actual proof of the efficacy of the form of therapy recommended must await a statistical comparison of the results before and after the use of this therapeutic regimen. In spite of many failures, however, it is agreed by all who have observed the patients treated that the results are far better and more consistently good than could be explained on the basis of the occasional spontaneous remission to be expected. Two cases will be described which are representative of satisfactory results.

**CASE I—History**—L. C., a 59 year old white construction laborer, was admitted to the St. Louis City Hospital on August 4, 1942 complaining of indigestion and postprandial bloating sensation of 3 weeks' duration. The patient denied nausea, vomiting, hematemesis or jaundice. Some ankle edema had been noted. The past history revealed the ingestion of two bottles of beer daily but no whiskey.

**Physical Examination**—The patient appeared to be his stated age. The abdomen was distended. Some evidence of weight loss was present but not marked. Chest and axillary hair were sparse. Few spider hemangiomas were seen about the chest and neck. Few basal rales were present bilaterally. The blood pressure was 114/78. Fluid wave, bulging flanks and shifting dullness were present. The liver was not palpable. Pitting ankle edema, grade 3 plus, was present. There was no apparent increase in venous pressure.

#### Laboratory Findings

RBC	$3.6 \times 10^6$	C-C Floc Test	4+
Hb	12.0 gm	Total Protein	7.3 gm %
Urine	Negative	Alb / Glob	0.9
Kahn	Negative	I V Hippuric Acid*	0.41 gm in 1 hr
Icteric Index	15	Bromsulfalein	15% retention

\*Measured as sodium benzoate. Values less than 0.80 are considered abnormal.

*Course and Treatment*—The patient was placed on the low fat diet, given 1 gm of choline, 1 tablespoonful of cod liver oil and 1 quart of skimmed milk daily. Salyrgan was given intravenously in 1 cc. doses at weekly intervals on three occasions.

Diuresis occurred over a period of approximately two months with marked clinical improvement and almost complete disappearance of the ascites and ankle edema. The patient was discharged October 22 1942 with instructions to return to the outpatient dispensary. Check of the laboratory data at this time revealed essentially the same findings as on admission except for an increase in the hippuric acid excretion to 0.96 gm.

*Follow Up*—During the following three months there were recurrences of some ascites but this cleared prior to February 1 1943 and has not recurred up to the present time. Laboratory data secured on May 19 1943 were as follows:

C.-C. Flocc. Test	Negative
Total Protein	7.7 gm %
Alb / Glob	1.9
Bromsulfalein	none
Icteric Index	4
L. V. Hippuric Acid	0.79 gm in 1 hour

The patient is now working six and seven days a week as a farm helper. He no longer takes the choline but does observe the dietary restrictions.

*CASE II—History*—E. B., a 72 year old white man, was admitted to the St. Louis City Hospital on July 27 1942 complaining of dyspnea, ankle edema and swelling of the abdomen of approximately eight months duration. The patient had consulted a physician in April 1942 who made a diagnosis of heart failure and prescribed digitalis. No improvement in the symptoms was noted. The patient consulted a second physician who referred the patient to a hospital for diagnosis. Abdominal paracenteses were done eight or ten times at approximately weekly intervals. The patient was discharged without any apparent improvement. He then applied for admission in this hospital.

The past history revealed chronic alcoholism of many years duration (6 to 7 bottles of beer and variable amounts of whiskey daily). Tarry stools had been noted several times.

*Physical Examination*—The patient was an obese white male of approximately stated age. There were bulging flanks, a fluid wave and shifting dullness. The liver was palpable 2 to 3 cm below the costal margin in the right midclavicular line. Hemorrhoids and a 3 plus pitting ankle edema were present.

#### Laboratory Findings

RBC	4.9 x 10 <sup>6</sup>	C.-C. Flocc. Test	3+
Hb	13.8 gm. %	Total Protein	5.9 gm. %
Urine	Negative	Alb./ Glob	1.2
Kahn	Negative	L. V. Hippuric Acid	0.45 gm.
Icteric Index	12	Bromsulfalein	20% retention

*Course and Treatment*—The patient was started on the diet and medication immediately. Abdominal paracenteses were done on August 3 15 and 27 approximately 5000 cc. being removed each time. No subsequent paracenteses have been necessary. The patient's clinical improvement was satisfactory and he was discharged October 16, 1942. The serum proteins had risen to 7.3 with an albumin-globulin ratio of 1.8 but other laboratory observations were unchanged.

*Follow Up*—The patient has been seen at frequent intervals up to the present time. He remains free of signs or symptoms.

## SUMMARY

Clinical observations as well as experimental data suggest, but do not prove, that human cirrhosis is primarily a nutritional disease characterized by numerous dietary deficiencies. Early fat deposition in the liver is accompanied by anorexia which results in increasingly severe malnutrition. Inadequate intake of protein and the vitamin B complex leads to further hepatic damage as well as renders the liver increasingly susceptible to toxic damage.

If liver fat can be mobilized and further deposition prevented, there is sufficient improvement in the patient's appetite to permit correction of the dietary defects. Choline, methionine and a low fat diet have brought about such changes in experimental animals. Clinical experiences suggest strongly that these observations are applicable to human cirrhosis.

A plea is made for the early diagnosis of cirrhosis. Moribund patients with profound liver destruction are obviously beyond the help of any conceivable therapeutic regimen.

## BIBLIOGRAPHY

- 1 Allan, F N, Bowie, D J., McLeod, J J R and Robinson, W L. *Brit J Exper Path.*, 5 75, 1924
- 2 Best, C H and Lucas, C C. *Vitamins and Hormones*, 1 1, 1943
- 3 Broun, G O and Muether, R. O. *J.A.M.A.*, 118 1403, 1942
- 4 Broun, G O., Muether, R O., Corcoran, P J V and Goldberg, L B. *Proc Central Soc Clin Research*, 16 30, 1943
- 5 Connor, C L. *J.A.M.A.*, 112 387, 1937
- 6 Connor, C L. *Am J Path.*, 14 347, 1938
- 7 Cushny, A R. *A Text-Book of Pharmacology and Therapeutics*, 10th ed Philadelphia, Lea & Febiger, 1934
- 8 Fagin, I D and Zinn, F T. *J Lab & Clin Med.*, 27 1400, 1942
- 9 Fisher, N F. *Am. J Physiol.*, 67 634, 1924
- 10 Fleming, Ralph G and Snell, Albert M. *Am J Digest Dis.*, 9 115, 1942
- 11 Gottardo, P and Winters, Wm L. *Am J Med Sc.*, 204 205, 1942
- 12 György, Paul and Goldblatt, Harry J. *Exper Med.*, 75 355, 1942
- 13 Herrick, F C. *J Exper Med.*, 9 93, 1907
- 14 Kaplan, A and Chaikoff, I L. *J Biol Chem.*, 120-647, 1937
- 15 Patek, A. J., Jr. *Proc Soc Exper Biol & Med.*, 37 329, 1937-38
- 16 Patek, A J and Post, J J. *Clin Investigation*, 20 481, 1941
- 17 Patek, A J, Jr. *Bull. New York Acad Med.*, 19 498, 1943
- 18 Post, J and Patek, A J, Jr. *Arch Int. Med.*, 69 67, 1942
- 19 Ratnof, O D and Patek, A J., Jr. *Medicine*, 21 207, 1942
- 20 Wade, Leo J and Richman, Ellen J. *Lab & Clin Med* (In Press)
- 21 Webster, Graham T. *J Clin Investigation*, 21 385, 1942
- 22 Editorial. *Nutrition Reviews*, 1 88, 1942-43

# DIAGNOSIS OF GASTRODUODENAL DISEASE

JOHN L. HORNER, M.D. \*

It was not so long ago that the physician, in diagnosing diseases involving the stomach and first portion of the duodenum, had to depend entirely on the history, physical examination and analysis of the stomach contents and stool. With the discovery that the intestinal tract containing barium could be indirectly visualized by roentgenologic examination, a tremendous forward step was taken. This method was further increased in efficiency by the addition of the filming fluoroscope, or "spot film." Within the past ten years the flexible gastroscope has come into common usage and, although there is still not complete agreement about the significance of all the changes seen in the gastric mucosa, this examination has added a great deal to the elucidation of difficult diagnostic problems. With the addition of the x-ray and gastroscopic examinations it is certainly a very small percentage of lesions in the gastroduodenal segment that escape detection.

It would be impossible in an article of this brevity to discuss all the lesions that may occur in the stomach and first portion of the duodenum, as well as those in the gallbladder, pancreas and other organs which may mimic them. I shall limit myself to the consideration of gastric carcinoma, uncomplicated peptic ulcer and gastritis, which are by far the most common, and together probably account for 98 per cent of the patients with organic disease in this segment of the gastrointestinal tract.

## HISTORY

There is a tendency, where dependable radiologic, laboratory and other aids are available, to minimize, consciously or unconsciously, the importance of taking an accurate and complete history. It is true that confirmation should be obtained, if possible, of all diagnoses made from the history and physical examination, but one should not depend entirely on the roentgenologic and gastroscopic findings. Aside from the fact that these aids are not everywhere so readily available that we can use them on every patient with a dyspepsia, they may occasionally lead us astray. For example, the radiologist may find a deformed duodenal bulb and report "duodenal ulcer," whereas in reality this "ulcer" has been healed many years and the patient's complaints are due to an entirely different disease. By a careful consideration of the history it is often possible to make the diagnosis with considerable assurance and

---

From the Department of Internal Medicine, Washington University and the Washington University Clinics, St. Louis, Missouri.

Instructor in Medicine, Washington University School of Medicine; and Chief of the Gastro-Intestinal Clinic, Washington University Clinics.

obtain additional help only when further events throw the diagnosis into doubt

**Ulcer**—The description of the typical symptoms caused by duodenal and gastric ulcer has not been improved upon since the last century. The sequence of pain-food-ease means peptic ulceration in a high percentage of cases, particularly when the pain, which is usually called "gnawing" or "burning," wakes the patient at one or two o'clock in the morning. Usually the discomfort occurs one to four hours after meals, is least before the morning and noon meals and worst before the evening meal and during the night, perhaps because the food intake, which stimulates the secretion of acid, is progressively greater during the day. It should be emphasized that in some patients the discomfort is minor, due in part at least to differences in pain threshold, and the sequence of events may be overlooked except under careful questioning. Relief by food, milk and alkalies is almost always admitted except when complications are present.

Two other factors appear in almost every ulcer history—chronicity and periodicity. The complaints have usually started years before and have appeared at infrequent intervals since. The free intervals, however, grow shorter as the story comes up to the present, and the periods of pain become longer. Flare-ups of pain may occur at any time during the year. The popular impression that recrudescences of ulcer activity usually appear in spring and fall is mistaken.<sup>1</sup>

It is impossible to differentiate between duodenal and gastric ulcer on the basis of time relationship to meals. The old teaching that gastric ulcer pain occurs an hour or so after meals and duodenal ulcer pain just before the next meal is not borne out by experience. The location of the pain, however, is helpful. In the majority of cases an ulcer on the gastric side causes symptoms in the left upper quadrant or left epigastrium, whereas on the duodenal side the pain is somewhat to the right of the midline. When the ulcer is at the margin of a gastroenterostomy stoma the distress is lower and to the left.

**Cancer**—It has been well said that cancer has no history. Certainly there is no typical history in early carcinoma. The syndrome of nausea and vomiting, weight loss and upper abdominal discomfort are symptoms of late cancer. Unless a malignant lesion is suspected when the symptoms are slight and vague it will too often be discovered when a palliative operation is the most that can be offered.

Probably the most frequent early complaint is anorexia. There may be vague epigastric distress, a feeling of fullness, belching and coated tongue. In some patients there will be epigastric pain, similar to that produced by ulcer, but usually less periodic and with inconstant relief by food. Difficulty in deglutition may indicate involvement by the lesion of the cardia. If there is weight loss, even though slight, associated with any of these symptoms, x-ray examination should be done.

**Gastritis**—Inflammatory changes in the gastric mucosa can, and do,

cause symptoms. How frequently they do is still a subject for disagreement. Gastroscoipists often find gastritis where the symptoms cannot reasonably be ascribed to this condition. On the other hand, we have seen many cases in which the course of the patient's distress closely followed the improvement in the mucosal changes. A discussion of this problem was reported in a recent symposium,<sup>2</sup> and several articles have appeared in the literature of the past few years, but many more controlled studies will be necessary before a sound basis for gastritic symptoms can be established.

The gastritis which appears to be most often associated with symptoms is the hypertrophic form, and the syndrome most frequently encountered is that mimicking ulcer.<sup>3</sup> Other findings may be vomiting, hemorrhage, bloating, sour eructations and heartburn. The ulcer symptoms are found often enough to warrant a suspicion of hypertrophic gastritis whenever the x-ray examination fails to demonstrate an ulcer.

Atrophic gastritis, or more properly gastric mucosal atrophy, may be associated with a syndrome of mild epigastric discomfort, anorexia, weakness, nervousness, sore tongue, numbness and tingling of the extremities.<sup>4</sup> The digestive symptoms may frequently be secondary, in the patient's mind, to the general ones. That this syndrome occurs in many cases of atrophic gastritis I have no doubt. It remains to be explained why the others are not so affected.

Superficial gastritis may at times cause dull epigastric distress, belching and sour eructations coming very soon after eating.<sup>5</sup>

Summary.—A careful and complete history will in many cases enable the physician to make a presumptive diagnosis, and in others will give a suggestive lead. In diseases involving the gastroduodenal segment the complaints are usually referred to the epigastrium, or at least the upper abdomen. When the sequence of pain-food ease is encountered an ulcer must be suspected first, then hypertrophic gastritis, then possibly cancer. When the symptoms are vague the diagnosis of cancer or gastritis must be considered as well as 'functional' dyspepsia, cholecystitis, and so forth.

#### PHYSICAL EXAMINATION

In the diagnosis of gastroduodenal disease the physical examination offers little or no information. In *peptic ulcer* a point of tenderness may be found. Tenderness in the right epigastrium suggests a duodenal ulcer, in the left upper quadrant or left epigastrium a gastric lesion, in the left paraumbilical area a marginal one. The finding of a mass, of course, makes the presumptive diagnosis of *neoplasm*. An enlarged, nodular liver, palpable supraclavicular node, or palpable rectal lymph nodes (rectal shelf of Blumer) indicates metastases already present and hence is confirmatory of gastric malignancy where the history is suggestive. In severe *gastritis* a diffuse tenderness in the upper abdomen, particularly on the left, is often present. With the atrophic

gastritis of pernicious anemia there may be an associated pallor of the skin, glossitis and evidence of spinal cord damage, such as impaired vibratory sense of the extremities, abnormal toe reflexes and disturbances of the position sense and gait

#### LABORATORY FINDINGS

**Gastric Analysis**—The analysis of the gastric contents was an important examination in the days before accurate x-ray and gastroscopic observations. Today it is of secondary importance, though it should not be omitted. An adequate test consists of the aspiration of the chyle after at least an eight-hour fast, the subcutaneous injection of histamine (0.25–0.5 mg. average) and the removal of 10-cc. samples thirty and sixty minutes later. All samples are titrated with 0.1 normal sodium hydroxide, with Topfer's reagent the indicator for free acid and 1 per cent phenolphthalein for total acid.

There does not appear to be any particular advantage in using the various test meals with fractional analysis that have been advocated, since the normal range of values found varies within wide limits. Where the x-ray examination is not readily available, however, the test meal may be used to detect gastric motor delay. Winkelstein<sup>6</sup> has recommended the use of an oatmeal gruel meal simultaneously with the injection of histamine and neutral red. The neutral red is excreted into the stomach only if acid is produced. With this technic he found that true achlorhydria (pH of 3.5 or more) occurred in only 2.2 per cent of a large group of patients of all ages, a much smaller percentage than that found using histamine alone. Nevertheless, Winkelstein's technic is useful primarily where it is important to determine absolute achlorhydria, and not as a routine in gastroenterology. The injection of histamine alone will determine whether the gastric mucosa is readily capable of producing free hydrochloric acid, and roughly, whether too much or too little.

The fasting gastric juice should also be examined for evidence of blood and exudate, the first suggesting definite organic disease in the stomach, though not helping in the differentiation, and the latter suggesting a gastritis. Blood due to trauma from the tube must, of course, be ruled out. Testing for the presence of excessive lactic acid and Boas-Oppler bacilli is helpful in determining the presence of pyloric obstruction due to cancer, since they are found only with the combination of obstruction plus low acidity.

In interpreting the results of the gastric analysis it is important to remember that in ulcer or carcinoma there are many exceptions to the "typical" findings. Some patients with a gastric cancer have normal or even high values, and there are ulcer patients who cannot be considered to have a hyperacidity. Consequently in any individual case the results of the acid analysis are only suggestive and must be fitted into the picture as a whole before they can have any significance. The

sole exception to this is the finding of histamine refractory achlorhydria in a patient previously considered to have a benign ulcer. Benign ulcers occur so rarely, if at all, in an anacid stomach, that this finding should outweigh others and lead to a recommendation for prompt surgery.

In *gastritis* the amount of acid found is, as in other conditions, variable. It may be high in hypertrophic gastritis. It may be low, or absent, in atrophic gastritis. That atrophy is not infrequently associated with normal acid values may be attributed to the patchy involvement of the mucosa, with sparing of some acid-bearing areas. Where the entire mucosa is affected, as in pernicious anemia, achlorhydria is the rule.

The chief value of the gastric analysis, then, is the detection of histamine-fast achlorhydria, particularly in younger individuals. This should *always* cause further investigation.

**Stool**—The presence of gross blood in the stool rarely suggests gastroduodenal disease. Occult blood, however, as demonstrated by the guaiac or benzidine tests, may confirm the presence of a lesion in this area. The test is not conclusive unless the patient has been on a meat-free diet for forty-eight to seventy-two hours.<sup>7</sup> A constantly found positive test occurs in carcinoma much more frequently than in ulcer, whereas uncomplicated peptic ulcer is associated with only intermittent bleeding.

#### ROENTGENOLOGY

In the diagnosis of peptic ulcer and gastric carcinoma the roentgenologic examination is usually decisive. In gastritis, though it may occasionally be suggestive, it is never conclusive.

**Peptic Ulcer**—The criteria for the diagnosis of gastric or duodenal ulcer are well established. Benign ulcer is most commonly seen in the stomach as a penetrating niche arising from the posterior wall near the lesser curvature above the angulus, and will rarely be missed. The chief difficulty consists in differentiating a benign from a malignant ulcer—a problem which will be discussed below. Where the ulcer is in the antrum or on the midposterior wall, not projecting beyond the outlines of the lesser curvature, it may be demonstrated with the patient in an oblique position or with compression of the stomach wall leaving only a small residue of barium in the niche itself. It is appreciated that a shallow ulcer could be impossible to demonstrate. Also if the niche is filled with thick mucus or debris it may not be seen.<sup>8</sup>

The radiologic diagnosis of duodenal ulcer frequently rests on persistent deformity of the bulb associated with irritability or localized tenderness. Unfortunately only indirect evidence of activity in the ulcer can be obtained in this way. Since the distortion of the lumen is due to spasm, edema or scarring, or a combination of these, a duodenal cap containing a completely healed ulcer often appears very similar to one in which there is a penetrating niche. Furthermore, a de



formity of the cap can result from disease outside the duodenum, e.g., from adhesions secondary to cholecystic inflammation, conversely there may be no distortion even when a crater is present. For these reasons it is important to utilize the filming fluoroscope, or "spot film," in all cases suspected of ulcer. With this device varying degrees of pressure may be applied over the cap at the same time the films are exposed. The



Fig 95—A, Roentgenogram of the stomach of a 44 year old white woman with typical ulcer symptoms of nine days' duration. The only feature suggestive of ulcer is an irregularity of the superior medial border of the duodenal cap. B, Spot film of same patient during compression of the cap revealing a penetrating ulcer niche.

worth of this procedure is well demonstrated in Figure 95. At the time when this patient's ulcer symptoms were most severe routine films showed little or no irregularity of the duodenal cap, whereas the spot film revealed a niche one centimeter in diameter. In subsequent examinations the niche was found reduced in size and in a few weeks was gone. This case, which can be duplicated in any gastroen-

terologist's experience, shows the importance of the spot film in detecting active duodenal ulcers and in following their course

How often can the ulcer niche be demonstrated? Certainly in gastric ulcer the diagnosis is rarely made without seeing the crater. In the duodenal lesion the percentage of the craters seen varies widely with the experience of the examiner, and the care taken. The German physicians, notably Berg, who devised this procedure, claimed their ability to demonstrate niches in the majority of cases.<sup>9</sup> In the United States increase in familiarity with the method has resulted in a marked increase in the percentage of craters visualized. We cannot, however, say 'No crater, no ulcer.' Where the mucosal defect is seen we know we are on safe ground. When it is not seen we may still make the diagnosis on the basis of the typical deformity associated with a typical ulcer history.

**Cancer**—When a constant filling defect is found in fluoroscopy or x-rays of the stomach the presumptive diagnosis is carcinoma. Actually there are many other types of space-occupying lesions, including benign tumors and bezoars. These at times have features which distinguish them from the polypoid carcinomas they imitate, e.g., absence of lobulations, fissures and ulcerations. Here again the spot film is of great benefit, although in this type of growth gastroscopy gives more information. The use of the spot film in detecting gastric lesions is shown in Figure 96, multiple polyps of the gastric mucosa are demonstrated which are not seen in routine films.

There is usually little difficulty, except in the very early stages, in diagnosing the infiltrative type of cancer. This lesion results in an irregularity which is constantly found on serial observations, is stiff 'moth-eaten,' and fails to transmit peristalsis smoothly. The lag in peristalsis is an important sign when present, but its absence cannot be completely relied upon as an indication of a normal stomach.

The lesions which offer the most difficulty are those in the antrum and some ulcers on the anterior and posterior walls of the stomach. Antral lesions may be caused by cancer, benign gastric ulcer, duodenal ulcer with antral spasm, hypertrophy of the pyloric muscle, hypertrophic gastritis and syphilis.<sup>10</sup> In some cases one can only hazard a guess as to the nature of the disease associated with a prepyloric deformity. Repeated roentgenologic observations may help. Gastroscopy frequently helps. Exploratory laparotomy and even subtotal gastric resection may occasionally be necessary to rule out cancer.

**Benign and Malignant Ulcers.**—I do not propose to discuss the question of malignant degeneration in benign gastric ulcer. This has been ably done by Palmer<sup>11</sup> and I believe, with him, that such a change has yet to be proved. The important point is to distinguish benign ulcers from malignant ulcers. There are several radiological features that are helpful. Most malignant ulcers are larger than benign ones, but in the individual case this point is of no help, as all of us have seen tremendous

ulcers which were proved benign by operation, as well as very small ulcers which were highly malignant. The location of the niche is important only if on the greater curvature, where benign lesions rarely occur.

The significant feature of a benign ulcer is smoothness of outline. The adjacent rugae are usually thick and stand out from the back-



Fig 96—*A*, Roentgenogram of the stomach of a 50 year old white woman with recurrent epigastric distress and vomiting for several years. The x-ray examination, performed at an excellent laboratory, did not reveal the source of the symptoms. *B*, Spot film of same patient with compression of the stomach, showing multiple gastric polyps. This film was taken after the polyps, together with severe superficial gastritis, had been discovered by gastroscopy.

ground, converging toward the niche. Frequently there is associated spasm, resulting in the "hour-glass" stomach. Tenderness to pressure is present but is of less value in distinction. The malignant ulcer will not show the above characteristics, and in addition may reveal the "meniscus" sign first described by Carmen over twenty years ago. This sign

depends on the fact that a malignant ulcer lies in the approximate center of a raised area, the tumor. Hence a tumefied border, the halo or meniscus, is seen encircling the crater. The convexity of the meniscus, originally emphasized by Carmen, is probably not important,<sup>12</sup> but the intraluminal situation of the crater is essential i.e., it does not project beyond the normal borders of the stomach but into the tumor itself.

### GASTROSCOPY

In the few short years since its popularization in this country by Schindler, gastroscopy has proved its value beyond question. Now that the initial scepticism of the many and subsequent enthusiasm of the few have been tempered by experience it is possible to evaluate the place of gastroscopy in diagnosis. The limitations of gastroscopy are well delineated. It is not in rivalry with the x-ray examination, and never can be, because of these limitations. It should be regarded only as an adjunct to roentgenology.

Gastroscopy is safe. With adequate preparation it is not uncomfortable, many patients preferring it to the introduction of the small tube for gastric analysis. In the hands of even a moderately experienced gastroenterologist the chance of injury, provided the known contraindications are observed, is negligible. A few years ago Schindler found by means of a questionnaire sent to all men known to do gastroscopy that in 22,351 examinations there had occurred ten perforations, with one fatality. Five of the perforations were attributed to the rubber sponge tip, since that time largely discarded.<sup>13</sup> I feel sure that a questionnaire circulated at the present time would show the percentage of accidents still smaller.

Gastroscopy, of course, should not be done when disease of the esophagus exists. A preliminary fluoroscopic observation of a barium swallow should be done if the history suggests any difficulty in deglutition, or if any trouble is experienced in passing the Ewald tube. The examination should preferably not be attempted at all with marked curvature or arthritis of the cervical or dorsal spine, with intractable cough or dyspnea, with aortic aneurysms or mediastinal tumor displacing the esophagus, or with severe heart disease.<sup>14</sup> In many of these cases gastroscopy can be done successfully, but a risk will be taken which could be justified only if the information to be obtained were absolutely essential. Another type of patient who had best be left alone is the person who is too apprehensive to be cooperative.

The limitation of the gastroscopic examination is that only the gastric mucosa can be seen, and not all of that. The duodenal cap cannot be observed, the pylorus itself is occasionally hidden, the lesser curvature of the antrum is frequently blocked from view by the overhanging angulus, a strip of posterior surface down which the gastro-scope slides is not visible, nor is the lesser curvature adjacent to the

cardia Despite these blind areas most lesions that can be seen by roentgenologic examination can also be seen by gastroscopy, and not infrequently an ulcer or small tumor may be detected which has evaded radiologic investigation<sup>15</sup>

There are several groups of cases in which gastroscopy is of definite value It should be done whenever symptoms are suggestive of gastroduodenal disease, even though x-ray films are negative It may be used to confirm positive roentgenologic findings in the stomach, and to help differentiate between benign and malignant lesions When the findings of the x-ray examination are suggestive of disease, the gastro-scope will provide additional information that may be conclusive

**Gastritis**—The presence of gastritis, other than by biopsy, can be determined only by gastroscopy Most roentgenologists agree that they cannot with certainty make this diagnosis, although occasionally the hypertrophic form may be suggested by thick folds and nodulations outlined by a small amount of a thick barium mixture<sup>16</sup> There is need, it is true, for better correlation of gastroscopic and pathological interpretation, but sufficient studies have been made to place the gastroscopic diagnosis of gastritis on a firm basis<sup>17</sup> It is to be hoped that the Kenamore biopsy forceps will be further improved so that bits of mucosa can readily be taken for pathological confirmation of the gastroscopic impression<sup>18</sup> Another method which will make for greater unanimity of interpretation is gastrophotography, which is now becoming practical<sup>19</sup> When color photographs of abnormal mucosae are commonly published it will quickly be determined whether various observers are talking about the same thing

Gastritis has been classified in various ways Most gastroscopists in this country adhere to the Schindler classification, which divides the inflammatory changes into superficial, hypertrophic and atrophic<sup>20</sup> There is essential agreement concerning the differential diagnosis of these forms, as evidenced by the approximately equal percentage of cases found in several large published series It appears, however, that the superficial and hypertrophic forms, in their lesser degrees of severity, may be confused.<sup>21</sup>

Superficial gastritis is believed to be present when the mucosa appears redder than normal, is edematous and shows patches of adherent exudate Small erosions and hemorrhagic spots are not uncommon

The diagnosis of hypertrophic gastritis is based on the finding of a dull, slightly swollen mucosa, lacking the usual highlights, with a nodular "cobblestone" or vermiform appearance The nodes at times may be large enough to resemble true polyps, and have a loose spongy character Small erosions and ulcerations are common

In atrophic gastritis the surface has a grayish color, the folds are few, and the branching network of blood vessels is visible due to thinning of the mucosa This is a picture which can hardly be mistaken Although some gastroscopists believe that excessive inflation of the

stomach with air may cause the blood vessels to be seen, the majority are not of this opinion.<sup>2</sup> Atrophy of slight degree, as with the other types, may be overlooked by the inexperienced.

**Cancer**—A typical polypoid malignancy is simple to identify through the gastroscope, although the distinction between carcinoma, sarcoma and other neoplasms may not be possible. The cancer appears as a necrotic mass projecting into the lumen. The limits of the growth and its blending into normal mucosa can usually be made out, and its extent may be found to be much greater than it appeared in the x-ray film. In any series of cases studied by both the x-ray and gastroscopic examinations there will be some cancers which can be seen by one method and not the other, which is the best possible argument for subjecting a patient with a suggestive history to both observations.

One of the chief advantages of the gastroscopic examination is the ability to elucidate the nature of a prepyloric narrowing found by the roentgenologist. As stated earlier, such a deformity may be caused by a variety of conditions, including simple spasm. In many such cases the entire antrum is well visualized gastroscopically, no mucosal abnormality is seen, and the patient is saved from an exploratory laparotomy. Or a simple hypertrophic gastritis may be found to account for the narrowing. However, one of the most difficult problems in gastroscopy is to differentiate a severe antral hypertrophic gastritis from a diffusely infiltrating cancer. In an occasional patient it may even be necessary to subject the patient to partial gastric resection because of the probability of cancer which neither the x-ray nor gastroscopic examinations can rule out. It should be emphasized nevertheless, that in the great majority of patients showing antral deformities an accurate diagnosis can be made by gastroscopy or at least the danger of intrinsic cancer dispelled.

**Ulcer**—Most gastric ulcers can be seen by gastroscopy, since they usually occur in the posterior wall near the lesser curvature above the angulus. As with carcinoma, both roentgenology and gastroscopy should be utilized, since some ulcerations are visible only by one or the other of these examinations. When an ulcer is directly visualized its course is best followed by repeated endoscopic observations, for it will be found present some days or weeks after it can no longer be seen by the x-ray examination. Duodenal ulcers, of course are detectable only by roentgenology.

Characteristically a benign ulcer is seen as a sharply punched out area with a clean gray or white base, or if penetrating deeply, as a black hole. The surrounding mucosa converges in folds toward the ulcer, may be red and edematous and slightly undermined, if no accompanying gastritis is present. Or it may show the changes diagnostic of superficial or hypertrophic gastritis, particularly if pyloric obstruction is present as a complication of the ulcer.<sup>22</sup> Tiny mucosal hemorrhages and brown pigment spots may be present, without gastritis.

**Benign and Malignant Ulcers**—Some authors have urged that all gastric ulcers be treated surgically on the basis that accurate distinction between benignity and malignancy cannot be made<sup>23</sup> It is true that occasionally the gastroscopist may be undecided after several observations, and then exploration should of course be recommended Rarely he may be mistaken But the mortality of major gastric surgery in most medical centers is certainly greater than the percentage of error by the experienced gastroscopist

There are a number of signs which have been found of value in indicating the malignant nature of an ulcer Of these perhaps the most important is blending of the ulcer floor with its wall<sup>24</sup> Even though most of the ulcer margin is sharp, if at one point it is not clear-cut a strong suspicion of cancer must be entertained Irregular nodes within the ulcer floor or in the adjacent mucosa, ulcerations in the wall immediately surrounding the ulcer, and bleeding of the ulcer edge are additional evidences of malignancy The location may be helpful, as benign ulcers rarely occur in the antrum close to the greater curvature, or involve the pylorus There are usually no converging folds in malignant ulcer

In addition to the typical punched-out character of the benign ulcer, Schindler feels that the presence of pigment spots and small mucosal hemorrhages away from the niche are evidence of benignity Henning, a pioneer European gastroscopist, has called attention to an arch-shaped deformity of the angulus as due to benign ulcer on the lesser curvature of the antrum, pulled up out of sight and hidden by the angulus This sign is of value mainly in tending to confirm a roentgenologic diagnosis

**Gastrointestinal Allergy**—Before closing this discussion mention should be made of gastroscopic confirmation of gastrointestinal allergy, a disorder which may mimic gastroduodenal disease Pollard and Stuart<sup>25</sup> have reported the changes seen through the gastroscope following the introduction of the suspected food These were hyperemia of the mucosa, edema, diminished peristalsis and the outpouring of quantities of grayish mucus, all involving mainly the lower one-third of the stomach Further study along this line should help greatly in understanding and diagnosing gastrointestinal allergy

#### SUMMARY

Recent developments in gastroenterology have made the diagnosis of gastroduodenal disease extremely accurate A careful history is important in determining what, if any, aids in diagnosis should be used Roentgenologic observation, particularly with the use of the spot film is the most important single additional examination Gastroscopy, however, is essential for the detection of gastritis, and is valuable in confirming positive roentgenologic findings, in differentiating benign and malignant lesions of the stomach, in further elucidating suspicious x-ray

findings, and in discovering an occasional ulcer or neoplasm that the x-ray examination has missed

## BIBLIOGRAPHY

- 1 Palmer W L. in Cecil R L. A Textbook of Medicine 5th ed., p 768 Philadelphia, W B Saunders Co
- 2 Carey J B et al. Gastroenterol., 1 264 (March) 1943
- 3 Benedict, E. B. Gastroenterol., 1 62-65 (Jan) 1943
- 4 Schundler R. and Murphy H M. Am J Digest Dis., 7 7-14 (Jan.) 1940  
Holland A. L. M CLIN NORTH AMERICA, 26 711-724 (March) 1942
- 5 Schundler R., Ortmayr M and Renshaw J F., Arch Int Med., 60 143 1937
- 6 Winkelstein A. Am J M Sc., 203 419-428 (March) 1942
- 7 Bockus, H L. Gastro-enterology Vol I p 411 Philadelphia W B Saunders Co., 1943
- 8 Kirklin B R. M CLIN NORTH AMERICA, 25 1117-1124 (July) 1941
- 9 Berg H H. Ergebn d. med Strahlenforsch 2 249-350 1926
- 10 Kirklin, B R. M CLIN NORTH AMERICA, 25 1125-1141 (July) 1941
- 11 Palmer W L. Ann. Int Med., 13 317 (Aug) 1939
- 12 Kirklin, B R. Am J Roentgen., 47 571-577 (April) 1942
- 13 Schundler R. Am J Dig Dis., 7 293 (July) 1940
- 14 Jankelson, I R. and McClure C. W., New England J Med., 224 64-67 1941
- 15 Templeton, F E. and Boyer R. C. Am J Roentgenol., 47 261-274 (Feb) 1942
- 16 Templeton F E. and Schundler R. Am. J Roentgenol., 41 354-376 (Mar) 1939
- 17 Swalm, W A. and Morrison L. M. Am J Digest. Dis., 8 391 1941
- 18 Kenamore, B., Am. J Digest. Dis. 12 539 (Dec.) 1940
- 19 Rafsky H A. Am J M Sc., 206 618-622 (Nov) 1943
- 20 Schundler R. Gastroscopy University of Chicago Press, 1937
- 21 Horner J L. and Scheff H. To be published in Am. J Digest. Dis.
- 22 Scheff H., Horner J L. and Kenamore, B. Gastroenterol., 3 506 (Dec) 1944
- 23 Allen, A. W. and Welch, C. E. Ann Surg 144 498-509 (Oct.) 1941
- 24 Schundler R. and Arndal O. Arch Surg., 44 473-488 (Mar) 1942
- 25 Pollard, H M. and Stuart G J. Allergy 13 467 (July) 1942



# DIAGNOSIS AND TREATMENT OF PLEURAL EFFUSIONS

ALFRED GOLDMAN, M D , F A C P \*

FLUID in the pleural cavity is a common clinical finding as a complication of both pulmonary and extrapulmonary disease. Rarely does it represent any primary lesion of the pleura. Usually the interpretation of the fluid is simple, as in the effusion occurring during the course of a pneumonia or an obvious pulmonary tuberculosis. Often, however, the diagnosis may be difficult and requires careful study of the fluid for a correct interpretation of the underlying disease. It is the purpose of this discussion to group together the various practical methods used in the study of effusions with particular reference to the gross and microscopic characteristics, and to outline the treatment of the important types. All known pleural fluids will be included. Symptoms and signs will not be discussed as these are common knowledge to all. The subject matter will be taken up under the headings of (1) thoracentesis, (2) clinical pathology of the fluid, (3) classification of pleural fluids and (4) treatment of important types.

## THORACENTESIS

The final diagnosis in the study of pleural fluids lies in the examination of the fluid itself. The *site of aspiration* should be carefully selected by physical signs and x-ray examination. This is especially important in interlobar, mediastinal and diaphragmatic collections of fluid, when it becomes necessary to take both upright and anteroposterior and lateral plates of the chest. Plates taken in the prone position are often misleading, as the fluid may spread over the entire lung field in this position. It has been generally assumed that pleural fluids do not move with change in position except in the presence of a complicating pneumothorax. Rigler<sup>1</sup> has shown, however, that pleural transudates and exudates of recent origin before adhesions have formed will shift considerably with change of position. The patient should be tapped while lying on his sound side. At times it may be necessary to have the patient in the sitting position, particularly in the presence of a hydro-pneumothorax or in cardiac decompensation.

The skin is prepared with iodine and alcohol, and an intracutaneous bleb is made using a fine hypodermic needle and 1 per cent novocaine. Then the deeper tissues are infiltrated down to the pleura with a No. 21 needle. Aspiration is then carried out using a 50 cc syringe and a

---

From the Department of Internal Medicine, Washington University School of Medicine, St. Louis, Missouri.

\* Assistant Professor of Clinical Medicine, Washington University School of Medicine.

long needle, size 18 to 14. While suction devices such as a Potain apparatus may be used, they are undesirable, as too rapid evacuation of fluid may produce chest pain, cough, syncope or even pulmonary edema. In handling large amounts of fluid, a two-way stopcock for withdrawal of the fluid into the syringe and then emptying it into the container should be used.

If untoward symptoms occur, aspiration is either discontinued or introduction of air into the pleural cavity, either with the syringe or preferably with a pneumothorax machine through a cotton filter, will usually stop the symptoms and aspiration may then be continued. The amount of air used should be about one-third of the fluid removed. Sometimes the introduction of air is desirable for diagnostic and therapeutic purposes, in which case it should be done at the time of aspiration. A pneumothorax is often of value in differentiating between pulmonary mediastinal and thoracic wall lesions.

#### CLINICAL PATHOLOGY OF PLEURAL FLUIDS

**A. Physical and Chemical Characteristics**—1 *Gross*—Fluids may be classified by their gross appearance as (a) serous or serofibrinous, (b) seropurulent or purulent, (c) hemorrhagic, (d) chylous or pseudo chylous, (e) cholesterous, (f) bile-stained, or (g) combinations of any of the above.

2 *Specific Gravity*—The specific gravity is of particular importance in the nonpurulent effusions. It at once classifies fluids into transudates or edema fluids, and exudates or inflammatory fluids. In general, the transudate has a specific gravity below 1.015, the exudate above 1.018, the malignant effusion about 1.017.

3 *Chemical Studies*—These are usually of little practical importance. In general, the protein content is roughly in direct proportion to the specific gravity. A specific gravity of 1.012 means less than 2 per cent protein (transudate), while a specific gravity of 1.018 means more than 4 per cent protein (exudate). Simple transudates usually do not coagulate while exudates generally do. A rough but simple estimate of the protein may be made with the Esbach albuminometer. The pleural fluid should be diluted 1 to 10 with distilled water. Estimation of the sugar content of the fluid has some value in the study of the effusions following artificial pneumothorax. A figure of over 70 mg per 100 cc. is a favorable sign indicating sterility, while one of under 50 mg indicates the presence of tubercle bacilli and a subsequent empyema formation (Nassau<sup>2</sup>).

4 *Cytology*—The study of the cells in pleural fluids is of particular importance in the nonpurulent effusions. The fluid should be citrated to prevent clotting, centrifuged and a portion of the sediment spread on a slide, allowed to dry in air, then stained with Wright's stain. In every undiagnosed case where there is a possibility of malignancy, the *section sediment method of Mandelbaum*<sup>3</sup> is an absolute prerequisite.

as tumor cells can be demonstrated in the majority of effusions due to a malignancy. The original method is as follows:

The fluid is placed in a large Erlenmeyer flask and allowed to stand over night in an ice-box. The supernatant fluid is decanted and the sediment poured in a large centrifuge tube and centrifuged for at least twenty minutes at moderate speed. The supernatant fluid is again decanted and the sediment hardened with a solution of 10 per cent formaldehyde or Zenker's fluid for twenty-four hours. The fixed sediment is then treated as ordinary tissue by running through alcohols, embedding in paraffin and staining with hematoxylin eosin. The final sediment is a little conical button, which is cut from the above down, so as to include all cellular elements. *Foot's*<sup>4</sup> *modification* is the addition of glacial acetic acid to bring the acid percentage to 2 per cent which prevents coagulation. The advantage of the section-sediment is that the cells in a large amount of fluid may be studied in their natural relationship to each other. The method is an excellent one to demonstrate all types of cells, as well as such unusual lesions as actinomycosis.

The following cells may be seen in pleural fluids:

1 *Polymorphonuclear Leukocytes*—These obviously predominate in all pyogenic infections.

2 *Lymphocytes*—A high proportion of lymphocytes is typical of tuberculosis. However, they are also present in large numbers in malignant effusions, tularemia and the effusion of Meigs' syndrome.

3 *Red Blood Cells*—These are present to some degree in most pleural fluids. Grossly bloody fluids may be classified as follows:

(a) *Hemothorax*. This is a mechanical bleeding into the pleural cavity due to the following causes:

1 Trauma of the chest

2 Rupture of an aneurysm or erosion of an intercostal vessel

3 Spontaneous idiopathic hemopneumothorax. This is an unusual disease occurring suddenly in young healthy males, probably due to the rupture of subpleural blebs and tearing of adhesions.

(b) *True hemorrhagic effusions*. These may be serosanguineous or frankly bloody. Approximately two thirds of all hemorrhagic effusions are due to malignant tumors (Berliner<sup>5</sup>). Next in frequency follows inflammatory lesions of miscellaneous types, tuberculosis and pulmonary infarction. Occasional rare causes are heart disease, rheumatic fever, blood dyscrasias such as hemophilia, purpura, scurvy and severe anemia, Meigs' syndrome, snake bite and heparin.

4 *Mesothelial Cells*—These are large cells with abundant cytoplasm and pale-staining nuclei. They are characteristic of the cardiac transudates. At times the cells may be swollen, degenerated and vacuolated.

and may be confused with tumor cells. Mitotic figures may even be present in nonmalignant effusions.

**5 Eosinophils**—It is not uncommon to find eosinophils in pleural fluids. They have been found in the following lesions: (a) hemothorax, especially during the clearing stage, (b) pneumonia, particularly in the recurrent pneumonias of the asthmatic, (c) tuberculosis, (d) following artificial pneumothorax for tuberculosis, (e) effusions due to malignant tumors, (f) hydatid disease, (g) pulmonary infarcts, (h) heart disease, (i) nephritis, (j) repeated pleural punctures, and (k) intrapleural injections of saline, gold salts or olive oil. The significance of eosinophils in such a wide array of diseases is not known. There is usually no relationship between the percentage of eosinophils in the fluid and that in the blood.

**6 Tumor Cells**—By the Mandelbaum method previously described, tumor cells can be demonstrated in approximately 60 per cent of effusions due to malignant tumors. The cells appear in the section in two forms: (a) Fragments of tumor tissue showing glandular or pseudo-glandular arrangements or clumps of tumor cells. These can be easily recognized. (b) Isolated tumor cells. These are large atypical cells with deeply staining eccentric nuclei, often with mitotic figures, the cells standing out conspicuously around the other cells in the sediment. They may be confused with degenerated endothelial cells. *Positive diagnosis on the basis of isolated tumor cells should be made only by the expert pathologist.*

**C Bacteriology**—All fluids, whether serous or purulent, should be studied bacteriologically. The empyema following a pneumonia may start as a clear effusion from which the pneumococcus or streptococcus may be obtained. Serous and serofibrinous exudates not due to any obvious cause are tuberculous in at least 80 per cent of the cases. Tubercle bacilli may be found on direct smear or in a larger number of cases by culture and guinea-pig inoculation, an essential procedure in all doubtful cases. Even when organisms cannot be demonstrated, the effusion should be considered as tuberculous in origin unless proved otherwise. Tularemia is an important cause of serous effusions, as 14 per cent (Blackford and Case<sup>4</sup>) of tularemic pneumonias have pleural effusions which may persist for months. *B. tularensis* can be recovered from the fluid by special cultural methods.

The most frequent cause of purulent effusions are the pyogenic organisms with the pneumococcus first, streptococcus next and staphylococcus third in the order of their frequency. Practically every form of pyogenic organisms has been recovered from empyemas. It must be emphasized that 5 to 10 per cent of all chronic empyemas are tuberculous. In the secondarily infected tuberculous empyema, mistakes are often made and tuberculosis is overlooked. A pyopneumothorax should always suggest its possibility. Another important cause of empyema is fungus infection which usually produces thick pus. The

most common fungus disease found is actinomycosis, then blastomycosis and occasionally streptothricosis. *Coccidioides immitis* has also been recovered from pleural fluids. On occasion the section-sediment has demonstrated fungi when the bacteriological examination was negative.

**D Serology**—Serological tests of pleural fluids are sometimes of value. In tularemia the fluid shows a high titer of agglutinins for *B. tularensis*. The Wassermann reaction may be positive in the occasional case of luetic effusion. Complement-fixation tests for tuberculosis are advocated by some and are said to be positive in the majority of tuberculous effusions (Ogawa<sup>7</sup>).

#### CLASSIFICATION OF PLEURAL FLUIDS

##### A *Noninflammatory Fluids—Transudates*

- 1 Hydrothorax
- 2 Hemothorax
- 3 Chylothorax
- 4 Cholesterothorax

##### B *Inflammatory Effusions—Exudates*

- 1 Pyogenic empyema
- 2 Tuberculosis
- 3 Mycotic infections
- 4 Parasitic infections
  - (a) *Echinococcus* cysts of pleura
  - (b) Pulmonary distomiasis (lung fluke)
  - (c) Ameba
- 5 Tularemia
- 6 Rheumatic fever
- 7 Disseminated lupus erythematosus
- 8 Polyserositis
- 9 Specific diseases rarely associated with pleural effusions

##### C *Effusions Due to Malignant Tumors of the Pleura*

##### D *Effusions of Meigs' Syndrome*

**A Noninflammatory Fluids—1 Hydrothorax**—This is a transudation of serous fluid into the pleural cavity. The fluid is clear, straw-colored, has a specific gravity below 1.015, has very little protein and few cells and is sterile. The most common causes of hydrothorax are (a) cardiac disease of all types with associated heart failure, (b) renal disease, (c) cirrhosis of the liver, (d) Banti's disease, (e) local venous obstruction by mediastinal tumors, aneurysms, and the like, and (f) terminal events in pernicious anemia, leukemia.

**2 Hemothorax**—The causes of hemothorax have already been discussed under cytology.

**3 Chylothorax**—This is an accumulation of milky fluid in the pleural cavity.

(a) *True chylous effusions*—The percentage of fat is high, creams on standing, clears on shaking with a fat solvent, contains many fat globules stainable with fat stains. The following are the important causes:

- 1 Trauma to thoracic duct
- 2 New growth or glands outside the duct or within the duct.
- 3 Parasitic invasions, *Filaria*, *Trichina*
- + Thrombosis of left subclavian vein
- > Perforating lymphangitis

(b) *Chyliform effusions* The chylous appearance is due to fat droplets from degenerating cells. The globules are smaller. It is caused chiefly by carcinoma or tuberculosis

(c) *Pseudochylous effusions* The fluid is milky but contains no fat globules. The cause of the milky fluid has been ascribed to a lecithin globulin (Wallis and Scholberg<sup>8</sup>) and also to calcium phosphate (West<sup>9</sup>). Blankenhorn<sup>10</sup> thinks that all the cases are due to very fine emulsified fat

+ *Cholesterothorax*—This is a rare type of effusion containing large numbers of cholesterol crystals which give the fluid a peculiar opalescent, bright, glistening appearance. It has been most commonly found in long-standing tuberculous effusions. The pleura is found to be very thick, acting as an impermeable membrane. Blood cholesterol is not increased in these cases

B *Inflammatory Effusions—Exudates.*—1 *Pyogenic Empyema*—*Empyema* is usually secondary to a pneumonia or a suppurative lung disease. It may also occur as a direct extension from a pericarditis, through the diaphragm from an abdominal abscess and from penetrating wounds of the chest wall. The pus is usually creamy yellow. The pus from different types of empyema varies sufficiently to be of some diagnostic value. While the pneumococcus empyema starts off as a serofibrinous exudate, it rapidly thickens up to a creamy-yellow pus. The streptococcus exudate is thinner, being characteristically like thin pea soup. It is slower in thickening up and when it does, it is a thick whitish-green pus. When the pus is dark brown and fetid, there is usually an associated mixed infection, often with anaerobes. Rarely gas bacillus may be present and bubbles found in the pleural fluid

2 *Tuberculosis*—Every case of pulmonary effusion which cannot be explained on any other basis should be considered as tuberculous. The vast majority of so-called primary or idiopathic pleural effusions are due to the tubercle bacillus. Unfortunately, the organism can only be found in about 30 per cent of the serous cases on direct smear, hence the importance of culture and guinea-pig inoculation. All tuberculous fluids have a high specific gravity above 1.020 and coagulate rapidly

Both the spontaneous effusions and those occurring after artificial pneumothorax may be classified as (a) nonpurulent and (b) purulent, and the latter subdivided into (1) true tuberculous empyema and (2) mixed infection. The nonpurulent effusions usually start as clear straw-colored to amber fluid with more or less fibrin. Varying amounts of blood may be present which may give the fluid a hemorrhagic appear-

ance Tubercle bacilli may be absent or present in small numbers The fluid may spontaneously disappear The lymphocyte is the predominant cell The serous effusion may go on to become an empyema and must therefore be watched carefully

The tuberculous empyema fluid is purulent in appearance but thin and yellowish and flows easily While many lymphocytes are usually present, polymorphonuclears may predominate, especially in the cases following spontaneous pneumothorax Tubercle bacilli can readily be found

In the mixed infection types, the fluid takes on the appearance of pyogenic empyema becoming thicker and containing many pus cells

3 *Mycotic Infections*—Fungus infections rarely produce massive pleural effusions However, the pulmonary lesions may spread to the pleura where abscesses form and on aspiration the fungi may be found when cultured The section-sediment as mentioned previously may show the organisms Pleural lesions due to fungi have been found in (a) actinomycosis, (b) streptothricosis, (c) blastomycosis, (d) sporothricosis and (e) primary coccidioidal infections and coccidioidal granuloma

4 *Parasitic Infections*—(a) Echinococcus cysts of the lung may rupture into the pleura or may form in the pleura The withdrawn fluid contains characteristic hooklets The disease is rare in this country

(b) Pulmonary distomiasis (lung fluke) is common in Japan and China It is occasionally associated with a pleural effusion

(c) Amebic infection of the pleura may occur as a result of rupture of amebic liver abscess through the diaphragm into the pleural cavity The resultant abscess usually ruptures directly into the lung and may be found in the sputum The pleural effusion which may result is first serofibrinous and sterile but may become purulent by secondary infection The cells are usually polymorphonuclears and eosinophils with few lymphocytes Amebae may be found in the fluid

5 *Tularemia*—Pleural effusion is common in pulmonary and typhoid tularemia It appears later in the disease, sometimes four weeks after the onset It may persist for many months and therefore is easily confused with tuberculosis Thirteen of ninety-five patients reported by Blackford and Case<sup>6</sup> had pleural effusion The fluid is slightly turbid, yellowish, with a specific gravity above 1.017 The total cell count is not high and lymphocytes predominate The diagnosis can be made by recovery by *B. tularensis* from the fluid, by agglutination titer of the fluid and patient's blood, or by inoculation of a guinea pig The latter should be done with care as there is a high incidence of tularemia in laboratory workers

6 *Rheumatic Fever*—Pleural effusion is not uncommon in rheumatic fever It may occur as a primary manifestation, often in association with pericarditis, as a result of pulmonary infarction, pneumonia

or cardiac insufficiency. The fluid is usually clear, slightly turbid and straw-colored. Red blood cells may be present in sufficient numbers to give it a sanguineous appearance. It clots quickly, contains varying numbers of polymorphonuclears, lymphocytes, endothelial cells and is sterile on culture. It is rarely present in large quantities.

7 *Lupus Erythematosus Disseminata*—In this disease there is a tendency to recurrent serositis. The pleural effusion that may occur has the characteristics of a serofibrinous exudate.

8 *Polyserositis*—The pleural effusion in polyserositis is associated with a pericardial and peritoneal effusion. Inasmuch as the usual cause is tuberculosis, the fluid has the characteristics of the serofibrinous effusion seen in tuberculosis.

9 *Specific Diseases* rarely associated with pleural effusions include (a) syphilis, (b) smallpox, (c) anthrax, (d) undulant fever, (e) meningococcus sepsis, (f) typhoid fever, (g) bubonic plague, (h) sarcoidosis and (i) malaria.

C *Effusions Due to Malignant Tumors of the Pleura*—Practically all tumors which invade the pleural and cause effusion are secondary. Occasionally one finds a malignant tumor which suggests a primary endothelioma of the pleura, though many pathologists doubt its existence. The fluid in malignant effusions is either straw-colored serous, serosanguineous or frankly bloody. As already stated, the majority of bloody fluids, particularly in the older age group, are due to malignancy. However, not more than half of malignant tumor fluids are bloody. The specific gravity averages 1.017. Tumor cells can be demonstrated in 60 per cent of all cases by the Mandelbaum method. If one excludes the effusions due to pressure on mediastinal vessels, the percentage is still higher. Such effusions are in reality transudates. Metastatic tumorous effusions arising from tissues other than the lungs almost invariably will show tumor cells.

D *Effusion of Meigs' Syndrome*—Meigs' syndrome is given an important heading in spite of its rarity in order to call attention to a very important type of effusion, knowledge of which is relatively recent. Moreover, it is difficult to classify it with any other effusion. The syndrome first reported by Meigs<sup>11</sup> in 1937 is that of a benign ovarian fibroma with pleural effusion and ascites. The fluid has the characteristics of a transudate. It is usually clear, straw-colored, rarely hemorrhagic, specific gravity of 1.016 to 1.018, albumin content is low, the cells are few in number and are predominantly lymphocytes. The cause of the effusion is unknown, but the recognition of the syndrome is extremely important as removal of the fibroma is curative of the entire picture. Deaths have occurred in unrecognized and unoperated cases. One must therefore keep the syndrome in mind in all unexplained effusions in the female. Ascites may be so slight as to be overlooked while the pleural fluid may be large in amount.



## TREATMENT OF IMPORTANT TYPES OF FLUIDS

A Noninflammatory Fluids—1 *Hydrothorax*—Treatment is directed primarily to the cause of the transudate. If the fluid is small in amount, it may be left to be absorbed spontaneously. If it is large enough to produce symptoms of dyspnea, cyanosis or displacement of the mediastinum, it should be aspirated.

2 *Hemothorax*—The essential treatment is early aspiration without air replacement. Unless there has been sufficient bleeding to produce pressure symptoms, aspiration is delayed to the second or third day following the hemorrhage. The blood is removed daily by aspiration until the pleura is dry. By limiting the amount of fluid removed to about 500 cc reactions are usually avoided. If they should occur, aspiration should be discontinued. Occasionally it may become necessary to introduce air if there is evidence of a recurrent hemorrhage of the lung or to counteract the feeling of tightness or pain in the chest which may result from aspiration. Massive clot formation occurs in about 5 per cent of cases (Carter and DeBakey<sup>12</sup>). Aspiration in such cases is difficult. The presence of large clots prevents the lung from expanding and would result in extensive fibrosis of the pleura and atelectasis of the lung. If, after several weeks, lung expansion has not occurred, the clots should be removed by operation sometimes with decortication of the lung and the chest closed up tight.

3 *Chylothorax*—Treatment is directed to the primary cause of the disease. Aspiration may be necessary because of pressure symptoms. Smith and Woliner<sup>13</sup> advocate the intravenous injection of the chyle back into the patient.

4 *Cholesterothorax*—Aspiration is done to clear out the pleural cavity in an attempt to assist expansion of the lung. The pleura usually remains very thick, inasmuch as a prerequisite of the formation of the crystals is a long-standing effusion, usually of several years' duration.

B Inflammatory Fluids—1 *Pyogenic Empyema*—Repeated aspiration of the pus occasionally cures an empyema, particularly in the child. Continuous closed drainage as described by Mozingo<sup>14</sup> and Hart<sup>15</sup> may be used. While many patients have been cured by closed drainage, there are many objections to the method and it should be used only when there is some contraindication to open drainage. Thoracotomy with removal of a portion of a rib is the procedure of choice. The most important principle in the surgical treatment of empyema is the selection of the time of operation. This should be done when the pus has become thick, as by this time adhesions have formed and usually the pneumonia has quieted down.

Penicillin is proving an invaluable aid in the treatment of the empyema due to the pneumococcus, streptococcus and staphylococcus. Daily instillations of 25,000 to 50,000 units directly into the pleural cavity are made. Prior to the injection of the penicillin, the pus is aspirated and the pleural cavity irrigated with normal saline solution.

In a few days the pus becomes sterile and thin, following which daily aspirations should be made. Thickening of the exudate with accumulation of much fibrinous material may necessitate thoracotomy. Apparently some cases of coccal empyema may be cured by penicillin, without surgical drainage (Tillet, Cambier and McCormack<sup>10</sup>)

2 *Tuberculosis*—All cases of tuberculous pleural effusions should be treated by the general methods of treatment of tuberculosis, namely, bed rest, fresh air and adequate diet. Small nonpurulent fluids will spontaneously absorb. Large accumulations must be removed and careful x-ray study of the lungs made. If there is obvious pulmonary involvement, air should be introduced and a pneumothorax maintained. If the lungs are not visibly involved, aspiration alone is indicated. Rest in bed should be maintained for several weeks after all fluid has disappeared and then the patient may be allowed up on graduated exercise. Obviously, in those cases in which there is considerable involvement of the lung, bed rest may have to be maintained for a much longer period.

The pure tuberculous empyema is treated first of all by repeated aspiration. Irrigation of the pleural cavity with normal saline or Dakin's solution is usually advisable. This can be done with a three-way stopcock by which one can aspirate pus, evacuate it, replace with air, and then wash out with saline (Matson<sup>17</sup>). This is done in 100-cc. amounts with final complete emptying of the pleural cavity and replacing with air.

If repeated irrigations do not control the empyema, the next step is the use of oleothorax. The oil used is gomenol either in paraffin oil or olive oil. Gomenol is a volatile oil which inhibits the growth of tubercle bacilli in 5 per cent concentration and staphylococcus in 10 per cent. A pleuropulmonary fistula is a contraindication to its use. This can be determined by the introduction of a few cubic centimeters of a harmless dye such as methylene blue into the pleural cavity following which the patient's sputum will be colored if a fistula is present. The production of an oleothorax is accomplished by repeated aspiration of the pus followed by replacement with 5 per cent gomenolized paraffin oil until the entire cavity is filled with oil. Complete details of the method are given by Matson.<sup>17</sup> In the majority of cases, thoracoplasty becomes necessary to control the empyema. This is done to completely obliterate the pleural space and thus get rid of the effusion.

In the mixed infection type, there is a complication of a pyogenic and tuberculous empyema. One may try a disinfection type of oleothorax using 10 per cent gomenolized olive oil.<sup>17</sup> If this fails, thoracotomy should be done first to drain the secondary infection, to be followed later by thoracoplasty.

3 *Fungus Infections*—Fungus infections are treated by wide surgical drainage and excision of diseased tissue. Large doses of potassium iodide are helpful.

Treatment of the remaining types of inflammatory effusions consist primarily of the treatment of the underlying disease and requires no special consideration

**C Effusions Due to Malignant Tumors**—These present a hopeless prognosis. Repeated aspiration may give the patient temporary relief. X-ray therapy is valueless. One must be certain that the effusion present in association with a tumor of the lung is caused by metastasis to the pleura, as such an effusion may be benign.

**D Effusion Due to Meigs' Syndrome**—In this rare and easily overlooked disease, removal of the ovarian fibroma results in a brilliant cure. The patient should be first prepared by aspiration of the pleural effusion.

#### SUMMARY

1 The important diagnostic methods in the study of pleural fluids are outlined. The most valuable procedures in the nonpurulent effusions are the determination of the specific gravity and the study of the cells in the fluid. The latter is best carried out by the section-sediment method of Mandelbaum. The significance of the various cells found in pleural fluids is given in detail. The bacteriology of the purulent effusions readily determines the underlying disease. Tuberculosis must always be kept in mind as a possible cause. Fungus infections occasionally invade the pleura and are readily overlooked unless specifically investigated.

2 All known pleural fluids are classified. Particular emphasis is laid on the effusions due to tuberculosis, tularemia, and Meigs' syndrome.

3 Treatment of the important types of pleural effusions is given.

#### BIBLIOGRAPHY

- 1 Rigler, Leo. *Am J Roentgenol.*, 25 220, 1931
- 2 Nassau, E. *Tubercle*, 22 249, 1941
- 3 Mandelbaum, F S. *J Lab & Clin Med*, 2 580, 1917
- 4 Foot, N C. *Am J Path.*, 13 1-12, 1937
- 5 Berliner, Kurt. *Ann Int Med*, 14 2266, 1941
- 6 Blackford, S S and Case, C J. *Arch Int. Med.*, 67 43, 1941
- 7 Ogawa, J. *J Immunol.*, 7 423, 1932
- 8 Wallis, R L M and Schölberg, H A. *Quart. J Med.*, 111 301 1910
- 9 West, S. *Trans Clin. Soc London*, 39 42, 1906
- 10 Blankenhorn, M A. *Arch Int. Med.*, 32 140, 1923
- 11 Meigs, Joe V and Cass, J W. *Am. J Obst & Gynec.*, 23 249, 1937
- 12 Carter, B W and Debaeky, M E. *J Thor Surgery*, 13 4-127, 1944
- 13 Smith, D D and Woliner, E. *Arch Surg.*, 43 626, 1941
- 14 Mozingo, A E. *Am J Med Sc.*, 161 676, 1921
- 15 Hart, D. *Arch Surg.*, 19 1732, 1929
- 16 Tillet, Wm., Cambier, M and McCormack, J E. *Bull N Y Acad Med.*, 20 142, 1944
- 17 Matson, R C. In *Goldberg's Clinical Tuberculosis* Chap 19 Philadelphia F A Davis Co., 1941

## DIFFERENTIAL DIAGNOSIS OF PRECORDIAL PAIN

JULIUS JENSEN M.D., PH.D. (Med.), M.R.C.S. (Eng.)  
L.R.C.P. (London)\*

With improving differential diagnosis the study of precordial pain becomes increasingly complicated. Our recent enthusiasm about "coronary pain" has for a while led us to overlook many conditions which now emerge as problems of differential diagnosis. Many patients seen in cardiological consultation practice do not have heart disease although their symptoms at one time or another may have been quite deceptive. In 1935 Herrick<sup>1</sup> listed no less than twenty-eight different conditions which had been mistaken for coronary thrombosis. Special papers have described many aspects of the problem, but because of its importance, it was thought worth while to review as a whole the various mechanisms of precordial pain and the various diagnostic difficulties involved in each one.

### MYOCARDIAL ANOXEMIA

We accept the concept that anoxemia of the myocardium is painful and is the cause of most pain arising from coronary disease, be it "angina pectoris of effort and of emotional tension," infarction of the myocardium or the less easily defined "coronary insufficiency."<sup>2</sup> We also agree that a similar mechanism probably is effective in a number of conditions in which the coronaries may be functionally intact. This would be feasible if the blood pressure for any reason is lowered to a point where it is unable to maintain an adequate supply of blood in the coronary system. If coronary disease interferes with arterial function such pain is, of course, brought on more easily. Anemia itself is not necessarily a cause of precordial pain, but it may facilitate its production by other factors. Sometimes lowering of the blood pressure causes precordial pain by an indirect mechanism, it favors thrombus formation in arteries which are atherosclerotic. This is the mechanism seen after operations,<sup>3</sup> and also after drinking ice water<sup>4</sup> which presumably leads to cooling and dilation of the coronaries near the esophagus and consequently to slowing of the blood stream with thrombosis. The low blood pressure may be at least partly responsible when hypotensive, hyposthenic persons complain of precordial pain on effort. Another similar cause of pain through inefficient blood flow

From the Department of Internal Medicine Washington University St. Louis, Missouri

Assistant Professor of Clinical Medicine, Washington University School of Medicine. Assistant Physician Barnes and St. Luke's Hospitals. Cardiac Consultant, St. Louis City and St. Louis County Hospitals.

is seen in marked tachycardia or in marked bradycardia. When tachycardia reaches the critical stage the diastolic phase may become too short for ventricular filling. Consequently, the stroke volume is diminished and the myocardial nutrition suffers. The resulting pain has repeatedly been confused with that of myocardial infarction. Anoxemia of hypercyanosis of mitral stenosis<sup>5</sup> may cause a pain which in all respects resembles that of myocardial infarction.

Myocardial nutrition may be impaired by actual *blocking of the coronary arteries*. This may be organic or, possibly, functional. Organic blocking of the coronary arteries may occur at their orifices, which may be blocked by vegetations or by syphilitic changes of the aorta. Syphilis of the coronaries themselves has been described but is rare. The typical coronary atherosclerosis and arteriosclerosis occurring along the course of the arteries gives rise to the classical angina pectoris of effort and of emotion. This is almost certainly a pain of relative ischemia brought about by failure of the coronary circulation to dilate sufficiently to carry the increased load of blood required for increased cardiac work. It is readily relieved by rest. The precordial pain of similar distribution in patients with known coronary disease, but occurring at rest, even awakening the patient from his sleep, is called pain of coronary insufficiency, which it almost certainly is, although the exact mechanism of its production is obscure. In its milder forms it may closely resemble the sensations of "heart consciousness" or "neurocirculatory asthenia." Perhaps in some cases the two conditions overlap.

It is thought that *spasm of the wall of the coronary arteries* can produce a similar pain, but that has not been definitely proved. The coronary arteries do possess vasoconstrictor nerves, and we know that smooth musculature generally is influenced by emotions. Striking examples of this are "spastic colitis" and emotional increases of blood pressure. Smooth musculature is almost certainly involved in other psychosomatic manifestations. Offhand there is, therefore, no reason why smooth musculature of the coronary arteries should not be involved in precordial pain arising from psychic conflicts.

If this mechanism does exist, it may be coexistent with two other mechanisms of unquestioned reality. One is the precordial pain which, in the presence of established coronary atherosclerosis is produced only by *emotional stress*. It seems almost necessary to assume the presence of some such functional factor when patients complain of pain when they get angry while a whole day's quail-shooting can be accomplished without discomfort.

The other mechanism is marked *lowering of the threshold of pain*. This will presently be discussed, but when severe precordial pain occurs in young hypersensitive persons under emotional strain, and the pain is projected along the very same cutaneous segments which carry the pain of true angina pectoris, it seems entirely likely that a spasm

of the coronary arteries as well as a lowering of the threshold to pain may be involved. Another observation which supports the conception of coronary spasm as a cause of precordial pain is the reflex change which may occur in the electrocardiogram when pain arising from some organ below the diaphragm is referred to the paths along which cardiac pain is generally projected. The simplest explanation of these changes is that the pain being referred to the cardiac nerves causes coronary spasm which in turn is responsible for the myocardial changes (ischemia) which affect the electrocardiogram.

It is, therefore, probable that coronary spasm may cause myocardial pain, and that the pain results primarily through myocardial ischemia. Whether the actual spasm may cause pain as it does for instance in gallstone colic is perhaps too obscure a question to be answered at this time.

#### SPASM OF SMOOTH MUSCULATURE

While it is not possible to establish that spasm of coronary musculature in itself causes pain there is no question but that spasm of smooth musculature elsewhere in the body may do that and that such pain may be referred to the precordium.<sup>6, 7</sup>

**CASE I**—A 65 year old white housewife had been nervous for a year. She had been under a psychiatrist's care in the hospital during April and May, 1943. About May 1, 1944 she began to get spells of pain beginning in the top of the epigastrium, radiating to the back and up the chest into both shoulders and into both arms. There was no known exciting cause they might come on any time of the day or night. On walking she sometimes got an oppressive feeling in the epigastrium. The pain would last forty five to seventy five minutes until she took empirin which relieved it. She suffered from gas and was relieved of her pain if she could pass it. The pain made her walk the floor and doubled her up. She did not vomit. She had indigestion following cheese and "7-Up." Anything eaten at night would give her trouble later on. Altogether she had twenty five attacks when first seen on May 7, 1944. She was referred by an excellent surgeon as a case of heart disease.

The physical examination revealed a well nourished woman with a blood pressure of 156/80 (later 176/82). The heart was normal transverse in position, the aortic shadow was wide and tortuous. The electrocardiogram was normal. The abdomen was slightly tender at the top of the epigastrium, but there was no tenderness over the gallbladder on repeated thorough palpation.

The patient was thought not to have heart disease. A ray of the colon showed spastic sigmoid colitis, for which she was treated. However, the symptoms persisted and became worse and on June 23, 1944 further x ray examination revealed gallbladder disease. Subsequent operation showed gallstones, she was improved following operation, and has had no more attacks.

Numerous similar cases may be found in the literature where they record many diagnostic difficulties and mistakes. Thus papers on the *differential diagnosis between coronary disease and gallbladder disease* have repeatedly appeared<sup>8, 9</sup> and the problem is far from being solved. The following factors contribute to the diagnostic problem: (1) Although the exact pathogenesis of neither of these conditions is known

an element of disturbed lipid metabolism is involved in both. They are both likely to occur in late middle age in overnourished persons. (2) Both of them are often associated with dyspepsia of varying degrees. (3) If in coronary disease the myocardium becomes insufficient the resulting congestion of the liver may produce pain and tenderness which may suggest gallbladder disease. (4) The pain of gallbladder disease may be referred over the precordium and in its severity (as in our case) may suggest heart attacks. If such patients are electrocardiographed during an attack, the electrocardiogram may show changes which suggest coronary insufficiency. These may clear up when the patient recovers. It remains questionable whether these changes are on an entirely functional basis or whether they reveal an otherwise latent pathologic state of the coronary circulation. (5) Finally, and most confusing is the fact that the two conditions may coexist in the same individual.

Precordial pain arising from heart disease shows an amazing variety in its cutaneous projection, which is difficult to explain. Fibers which have already carried pain due to other causes are predisposed to project heart pain when it occurs. Boas<sup>9</sup> has made some interesting observations in this field. In a patient with angina pectoris and with an abscessed tooth, the anginal pain would radiate to the affected tooth (Mackenzie). Anginal pain in the neck may be associated with arthritis of the left shoulder, anginal distribution in the lower part of the chest and upper abdomen may be associated with peptic ulcer or gallbladder disease. On the other hand, a patient who has both gallbladder disease and coronary disease may feel pain over the precordium which otherwise has the characteristics of pain arising from gallbladder disease. This brings up the interesting but as yet unanswered question as to whether such location of radiation is a first evidence of coronary disease, so far subclinical. All of these considerations necessitate extreme caution in differential diagnosis in cases presenting unusual features.

#### DIRECT IRRITATION OF NERVES

Direct irritation of the cutaneous nerves along which cardiac pain is usually projected may produce a clinical picture closely resembling heart disease. The literature contains many such cases. The most common cause of error is *arthritis of the spine*, pinching the nerves.<sup>11</sup> This pain may be affected by exercise and may be severe. Whenever pain projected along the thoracic nerves does not sound quite typical of angina pectoris, x-ray examination of the thoracic spine is indicated.

Another less common cause of error is *herpes zoster*, as illustrated in the following case report.

CASE II—The patient, a 63 year old woman, had previously been well except for asthma which was well controlled by various remedies. Her mother died in a heart attack. On the night of September 11, 1944 she developed suddenly a severe pain in the left side of the chest, especially over the upper sternum, and

radiating into the left arm. The pain was very severe and kept her awake most of the night. It was oppressive and at the same time burning in character waxing and waning at times becoming exceedingly severe. The next day she felt better but with the coming night it again increased in severity. She felt compelled to awaken her husband who called their physician at 4 00 A.M. On his arrival the pain had subsided somewhat and the patient looked remarkably well. There was no dyspnea. The blood pressure was 164/86, the heart rate 76 with regular rhythm and the sounds of good quality. The lungs were clear and there was no tenderness anywhere. Because of the distribution and character of the pain it was thought that she had suffered a myocardial infarction and she was admitted to the hospital the following morning. During the next two days she felt well, and slept most of the time. Only once did the pain threaten to return and it was promptly controlled with codeine. The electrocardiogram was normal, temperature, blood count and sedimentation rate remained normal. On the morning of the 15th she was found to have a typical rash of herpes zoster extending over the left chest and down the inside of the left arm.

In this case there is no reason to believe that the patient had heart disease, but cases have been reported (Spillane and White<sup>12</sup>), in which herpes zoster and heart disease have coexisted.

In this connection must be mentioned certain obscure cases of neuralgia of the thoracic nerves which are difficult to explain. Neuralgia, however, should remain a "back to the wall" diagnosis after all other possibilities have been exhausted. Myositis of the muscles of the neck and about the thorax have also been mistaken for heart disease.

#### IRRITATION OF SEROUS MEMBRANES OF THE CHEST

*Mediastinal emphysema*,<sup>13</sup> *inflammation of the serous membranes of the mediastinum, of the pleura and of the pericardium*<sup>14</sup> have all been mistaken for pain of coronary origin, especially myocardial infarction. One difficulty is that myocardial infarction, extending to the surface of the heart, may cause pericarditis. Also, pericarditis may in turn affect the underlying myocardium and the resulting electrocardiographic changes have been mistaken for those of myocardial infarction which they may closely resemble. Only in recent years have the electrocardiographic changes of pericarditis been recognized as having specific features which separate them from those of myocardial infarction. It is not uncommon to see young persons with pain in the chest which was thought to arise from myocardial infarction, but which really was a symptom of pericarditis. Weinstein<sup>15</sup> has recently published a series of cases which emphasize the difficulty involved in differential diagnosis. The difficulty is further complicated by the possibility that acute respiratory streptococcal infections may be associated with rheumatic endarteritic changes of the coronaries which in some cases may be related to the more typical forms of coronary disease (Weinstein, *loc cit*). It is obvious that we are dealing with a large field which is inadequately explored and which is filled with possibilities of diagnostic errors.



*Pulmonary thrombosis*, often complicated by pleurisy, may cause electrocardiographic changes which strongly resemble those of posterior infarction. The changes are thought to be due to reflex spasm of the pulmonary vascular bed which places sudden excessive strain on the right ventricle. Aggravation of the pain on respiration is a valuable but not conclusive symptom favoring inflammation of the pleura. Acute pericarditis occurs typically in young persons who have previously been well, very often the pain is preceded by a cold. There then follows a sharp precordial pain, often aggravated on deep inspiration. If the condition begins as a mediastinitis there may be pain behind the sternum and on swallowing. There follows a rather severe febrile reaction with temperatures somewhat higher than are seen in uncomplicated myocardial infarction. Often the characteristic changes in the electrocardiogram and the development of pericardial effusion will establish the diagnosis. This picture may closely resemble that of myocardial infarction in young persons.

CASE III—A 52 year old insurance executive who had previously been well attended a heavy business luncheon on August 9, 1944 following which he was indisposed. In the afternoon he developed severe abdominal pain which was diagnosed appendicitis and an appendectomy was performed that evening. Convalescence was uneventful and on the 18th he was allowed out of bed. Having been up about twenty minutes he felt faint, developed a sense of constriction about the chest, and dyspnea. There was at no time cough. A heart attack was suspected and an electrocardiogram was taken, it showed certain abnormalities which were interpreted as indicating myocardial infarction and the patient was treated accordingly. During the next five days the pain returned and he had some fever. He continued to be short of breath, but had no cough.

On August 23 the patient was admitted to the hospital where he arrived after a 100-mile ambulance ride. He was very sick with extreme dyspnea and vomiting. He subsequently quieted down and felt well except for dyspnea. On the 24th he had a pain across the right chest and soon another one in the left chest where a friction rub was heard. The electrocardiogram taken in the hospital similar to the one taken before, showed pathologic changes but not which were considered characteristic of infarction. An x-ray examination showed a definite enlargement of heart and shadows through both lung fields, suggestive of pulmonary infarction. The diagnosis was postoperative pulmonary infarction. For the next week he was comfortable, free from pain and fever and on September 3 he was returned home for further care. On September 4 he suddenly became worse with dyspnea and precordial pain and he died that afternoon. Autopsy showed a recent massive thrombus of the left pulmonary artery, several pulmonary infarcts, but no myocardial infarction.

#### PAIN ARISING FROM STRETCHING OF TISSUES

The stretching of various tissues in the body, even to the point of rupture, may be associated with a severe pain which may be ascribed to heart disease. This mechanism operates in a variety of disorders. Most dramatic is rupture of the aorta, sometimes with the formation of a dissecting aneurysm.<sup>16</sup> The clue to the correct diagnosis lies in the proper evaluation of the history and symptoms. The stretching at

tearing associated with the occurrence of pneumothorax,<sup>17</sup> have been mistaken for myocardial infarction. Abdominal organs, especially the stomach, may give rise to symptoms in a similar manner. Stretching of muscle must be the explanation of the pain arising from diaphragmatic hernia<sup>18</sup> or even from the acute distention resulting from dietary indiscretion.

CASE IV—This 49 year old merchant was invited to a spaghetti feast on June 10 1944. In anticipation of the meal, he ate very little during the day but about 8 o'clock he sat down to a large and rich repast. In the course of the meal he had five good-sized hughballs. On getting home about midnight he felt nauseated, but managed to get to sleep. He awoke at 2 30 and felt thirsty. He drank two glasses of ice water and went back to sleep. At 7 30 he awoke with a 'terrific' pain across the epigastrium. baking soda and an enema increased the pain. He induced vomiting but the pain persisted. A hypodermic injection of morphine failed to relieve the pain. additional medications put him into a stupor which deepened into sleep from which he awoke the next morning when the pain was gone. A local consultant, a man of excellent judgment, and the family doctor were uncertain of the diagnosis. Electrocardiograms taken on June 14 and about July 20 and on August 22 were all alike and within normal limits. There was some widening (near 0.10 sec.) of the QRS complex, with a very shallow Q<sub>1</sub> and slurring of the downstroke of R. S-T segments and T waves were definitely normal in all leads.

As a matter of precaution, but not of conviction, he was treated as having had a myocardial infarction, although he had no more symptoms of any kind, neither cardiac nor digestive.

A physical examination on August 22, 1944 showed the heart to be transverse in position, but not enlarged. The action was regular with a rate of 90. There were no murmurs and the blood pressure was 112/70. The physical examination of abdomen was normal.

Though the possibility that he had had an infarction cannot be excluded there was no suggestive evidence other than the pain, for which, however, another satisfactory explanation was available.

In such cases the differential diagnosis can be exceedingly difficult, it may in the last analysis be impossible to exclude one or other condition with certainty. Although the diagnosis of *acute indigestion* has lost favor, having so often led to the serious mistake of overlooking myocardial infarction, it still remains as a clinical entity which may closely resemble myocardial infarction.

The stretching of tissue may involve the heart itself, without infarction taking place, though the resulting pain may be immediately caused by ischemia. It has been suggested that such stretching occurs in the right ventricle in right ventricular strain and it is possible that some form of injury to the myocardium may result from acute heart strain and also from traumatic injury to the chest wall. This latter condition has medicolegal aspects which have been extensively discussed in the literature.

CASE V—A 22 year old factory worker was splitting cables to test their strength. Generally this was well within her capacity but on November 27 1943 one cable demanded an unusually hard pull and when it came apart she felt a

pain which extended from the second left intercostal space close to the sternum to the apex area. In the afternoon she developed breathlessness and the pain returned without effort on her part. This condition persisted to a varying degree during the next few days. Medical examinations at the time failed to reveal subjective findings and she gradually recovered as long as she did not exert herself.

However, on effort and under emotional strain she would develop a feeling as if her heart "drew up," she would get short of breath, her heart would beat fast and she would develop a "nervous chill." She would get such attacks at irregular intervals. They prevented her from holding a job up to the time of the examination (September 18, 1944).

There is now a compensation suit involved in the case.

The physical examination was entirely normal. The heart was well within normal limits as to size and shape. The heart rate was 84 and the rhythm regular. Over the pulmonic area was a soft systolic murmur and the electrocardiogram was entirely normal.

Realizing that this patient's symptoms may possibly have been aggravated by the consideration of compensation, this case must nevertheless be considered one of *effort syndrome*.

CASE VI—For five years this 42 year old doctor's wife had had attacks of viselike precordial pain radiating along the inner surface of the left arm.

The pain would come on once or twice a month, especially near her menstrual periods, at any time during the day or night, it could be caused by fright, scare or worry. Sometimes it was relieved by nitroglycerin, sometimes codeine was required for its relief. She was allergic to many things and had suffered migraine headaches.

She had been to several heart specialists and clinics without other satisfaction than a negative cardiac diagnosis which left her with her pain.

The physical examination on February 22, 1938 revealed a heart normal on fluoroscopic examination, a blood pressure of 142/84, pulse of 80 and no murmurs. The electrocardiogram was normal.

While she was in another room being prepared for fluoroscopic examination her husband told the physician that the first time she felt the pain was once when they returned from a party to find their home in flames with the children asleep on the second floor. Her reaction to this experience had been a severe precordial pain, which she henceforth felt whenever she became excited.

She was then treated by psychotherapy.

On March 3, 1939 her husband wrote "I am pleased to report that she is feeling fine just so long as she does not overexert herself and avoids worry."

#### THE THRESHOLD TO PAIN

In the evaluation of all of the conditions discussed in this paper the matter of the threshold to pain is important. It determines the severity with which the patient complains and it varies greatly from person to person, being influenced by the general state of the patient. It is lowered by previous pain and fatigue, raised by vigor and good health. Any given nerve path can be trained to become more sensitive if the patient focuses his attention on it, consequently, patients who watch for evidence of heart disease are more likely to feel it, irrespective of whether the impulses traveling along the nerve paths are physiological.

or part of organic heart disease. When complaints of precordial pain as a simple result of fatigue and introspection occur in hyposthenic or nervous persons in whom a physical examination reveals normal cardiovascular findings, the diagnosis of neurocirculatory asthenia is easy, but when such complaints occur in persons who must be suspected of or are known to have organic heart disease, it may be extremely difficult to determine how much of the patient's complaint can be treated lightly. In the following two cases it is not clear how great a part was played by the hypersensitiveness of the patient's nervous system.

**CASE VII.**—This 47 year old lawyer of French descent was high strung and emotional. His brother whom he frequently saw was suffering from frequent and severe attacks of angina pectoris.

He consulted a physician because one year ago he had suffered occasional precordial pains. The pains across the chest were just severe enough to cause him to rest and would leave in two to three minutes. There were also sharp pains about the left clavicle. These symptoms disappeared but returned at the beginning of the year and have persisted since. They sometimes were brought on by walking but emotional strain did not seem to affect them.

The patient was of sedentary habits and smoked thirty to forty cigarettes a day.

The physical examination on May 19, 1944 was entirely normal. His blood pressure was 108/84. His heart shadow was well within normal limits and his electrocardiogram was entirely normal.

Thus there was nothing on which to base a diagnosis other than a rather typical history. The conclusion was that this patient's complaints were probably psychogenic but that a final diagnosis should be deferred.

**CASE VIII.**—A 40 year old insurance man, who weighed 215 pounds, was highly strung and overindulged in both food and alcohol. He had for two years complained of an ache in his left pectoral muscle. This ache was never severe, it came and went periodically more so after overindulgence and heavy smoking. Over the last two years the pain had not changed appreciably and it was not affected by physical strain or emotion.

Two weeks ago his business partner suddenly dropped dead with heart disease and this caused him to look into his own condition.

When seen on August 16, 1944, he appeared a large, pot-bellied looking man. The heart was definitely of normal size and outline under the fluoroscope. The action was regular with a rate of 88. No murmurs were heard. The blood pressure was 118/96. The electrocardiogram was normal (transverse heart).

The man was highly sensitive and all findings were near or within normal limits. Yet he had a slight increase in diastolic pressure and he presented the general appearance which one frequently sees associated with coronary disease at a somewhat later age.

The diagnosis was early diastolic hypertension and cardiovascular hypersthenia, but close observation for further developments was recommended.

Even trivial complaints should always be taken seriously in patients who are known to have coronary disease (especially if they have previously had an infarction) and who have been fairly free of symptoms in the recent past. These symptoms may be the harbingers of a violent eruption as is shown by Case IX.

CASE IX—This 50 year old artist had a very severe posterior infarction eighteen months before his death. Following his recovery he was in reasonably good health though he passed through periods of threatening left ventricular failure. At no time prior to his death was there evidence of any other infarction. When seen in June he had few symptoms and during the next three months felt exceptionally well. He resumed his work of etching and was very productive in his studio which was on the second floor. On September 17 and 18 he did not feel quite so well and complained of little sticking pains around his chest. On the morning of the 19th he woke at 7:00 A.M., early for him, with indefinite complaints of dyspnea and restlessness. When seen at about 3:00 P.M. he had no particular complaints, but he did not feel inclined to climb his stairs until he had been reassured.

The physical examination was entirely normal and there were no changes in the electrocardiogram since June 30 except slight T wave changes in the chest leads, which were ignored as such changes are frequently seen in patients with coronary disease. He was discussing his future plans including travel to Paris after the war. At 3:30 P.M. he left the physician's office with his usual brisk walk. About five o'clock his physician received an urgent call to his home and arrived a few minutes later to find him moribund, yet mentally clear, stating that he was dying. He died a few minutes later.

### CONCLUSION

The purpose of this presentation has been to emphasize the multiplicity of conditions which give rise to pain over the precordium which can be mistaken for heart disease. Not until the history is complete and the objective evidence has substantiated the diagnosis can it be considered certain. The clinician must always approach the problem with the thought in mind that precordial pain need not mean coronary disease. Especially in young persons should coronary disease and myocardial infarction not be diagnosed on insufficient evidence. Since coronary disease has serious prognostic implications and should cause for important modifications of the patient's life, while other causes may be comparatively trivial and unimportant.

### BIBLIOGRAPHY

- 1 Herrick, J. B. J. M. Soc. New Jersey, 32:590 1935 (fr. White)
- 2 Master, A. M., Dack, S. and Jaffee, H. L. Modern Concepts of Cardiac Disease, Vol. 10, No. 11, 1941
- 3 Master, A. M., Dack, S. and Jaffee, H. L. Modern Concepts of Cardiac Disease J.A.M.A., 110:1415 1938
- 4 Luten, D. Am. Heart J., 7:36 1932
- 5 Burgess, A. M. and Elliss, L. B. New England M. J., 226:937 1942
- 6 White, P. D. Heart Disease 3rd ed. New York, The Macmillan Co., p. 504
- 7 Boas, F. P. and Levy, H. Am. Heart J., 14:540 1937
- 8 White, P. D. *Op. cit.*, p. 503
- 9 Boas, F. P. and Levy, H. *Loc. cit.*
- 10 Mackenzie, J. Heart, 2:265 1911
- 11 Hanflug, S. S. J.A.M.A., 106:523 1936
- 12 Spillane, J. D. and White, P. D. Brit. Heart J., 1:791 1939
- 13 Hamman, L. Bull., Johns Hopkins Hosp., 64:1 1939

- 14 Scherff, D and Boyd, L. J Clinical Electrocardiography Philadelphia, C. V Mosby Co., 1940, p 130 White, P D.. *Op cit*, p 504
- 15 Weinstein, J.. Ann Int. Med., 21 252 1944
- 16 White, P D.. *Op cit*, p 504
- 17 Herrick, J B *Loc cit*
- 18 Jones, C. M New England J Med., 225-963 1941

# THE CLINICAL USE OF DIGITALIS PREPARATIONS

J K LEWIS, MD \*

THE fundamental principles governing the proper use of digitalis are the same today as they were when first laid down by Eggleston<sup>1</sup> almost thirty years ago. New preparations, usually pure glucosides derived from various sources, have become available. These are effective preparations and have a definite place in therapy but in the majority of patients the drug of choice is the crude drug. Regardless of the preparation used, however, a knowledge of the general principles of digitalis therapy derived from studies on the crude drug and an appreciation of its virtues are essential if one is to obtain its full benefit.

## ACTION OF DIGITALIS

A detailed account of the pharmacologic action of digitalis is beyond the scope of this discussion and may be found in the general references listed in the bibliography and in a recent paper by Gold and Cattell.<sup>2</sup> One should recognize that the action of digitalis on the heart is of two kinds, the first an effect on the rhythm of the heart which is brought about by vagal effects and by direct action on the conduction tissues of the heart, the second a direct effect on the heart muscle. The first effect is responsible for both the favorable and unfavorable effects on cardiac rhythm, the second for the over-all increase in the efficiency of the heart as a pump. Because of these different actions digitalis is useful in both arrhythmias and in failure, and when the two are combined.

## USE OF DIGITALIS IN HEART FAILURE

**General Indications**—With few exceptions digitalis may have a beneficial effect on heart failure. It is effective in failure with peripheral edema and venous congestion as well as in failure manifested mainly by attacks of pulmonary edema. It is most effective in failure associated with auricular fibrillation and a rapid ventricular rate. It is also effective when there is sinus rhythm<sup>3, 4, 5, 6</sup> and, although the chances of success are not as good as in the case of auricular fibrillation, spectacular responses are sometimes obtained. With sinus rhythm its effectiveness may be related to the nature of the underlying heart lesion but evidence on this point is not strong enough to bar its use with any of the ordinary varieties of cardiac lesions. Marvin<sup>4</sup> found it most effective in arteriosclerotic heart disease while Wood<sup>6</sup> found it most

From the Department of Medicine, Stanford University School of Medicine, San Francisco, California

\* Associate Professor of Medicine, Stanford University School of Medicine

effective in rheumatic heart disease. It is probably ineffective in most instances of acute myocarditis but beneficial effects have been observed in the treatment of heart failure associated with acute rheumatic myocarditis. Its chances of success are poor in heart failure associated with constrictive pericarditis when there is sinus rhythm and it should not be used in treating the typical form of beriberi heart.

**Indications Under Special Circumstances**—There are special circumstances such as auriculoventricular block, coronary artery disease with angina pectoris or myocardial infarction and cardiac complications occurring with hyperthyroidism, acute infections or surgical procedures in which there may be some doubt about the advisability of using digitalis. Here again the presence of heart failure is the determining factor, but these situations deserve further comment.

Heart failure associated with all degrees of *auriculoventricular block* has been successfully treated with digitalis.<sup>7 8 9</sup> Apprehension over its use in these situations arises from fear that digitalis through its effects on conduction will increase the degree of block or precipitate Stokes-Adams attacks. Precipitation of Stokes-Adams attacks would contraindicate its use, but it is doubtful if slowing of the rate through increase in the degree of block would have an unfavorable effect. In complete block the drug is usually considered to be safe since no further change in conduction can take place. However, in three patients with failure and complete block Schwartz<sup>8</sup> reported fainting attacks in two and spells of unconsciousness in one during treatment with digitalis. All were deliberately given more than the usual dose of digitalis but this report suggests that it is not entirely free of danger under these circumstances. In partial block one might anticipate trouble since Stokes-Adams attacks may occur with an increase in the degree of block, a change which would be favored by digitalis. However, Blumgart and Altschule<sup>9</sup> systematically digitalized a group of patients with partial block and did not observe untoward effects. In sixteen of the nineteen patients in their series the degree of block was limited to a delay in conduction. Campbell<sup>10</sup> in observing block due to digitalis in a large series of patients noted no unfavorable effects. In this clinic one patient reported syncopal attacks during the course of 2:1 block induced by digitalis, and in a few ambulatory patients with complete block and mild failure spells of faintness and of palpitation have been reported by the patient during the administration of the drug. It seems likely therefore that digitalis may occasionally induce unfavorable effects in patients with various degrees of block, but when the chance of producing undesired effects is weighed against the possibility of relieving heart failure the decision must be to use it. It should be given with caution. A week or longer should be taken to digitalize the patient and he should be observed with more than ordinary care.

The indications for digitalis in heart failure in patients with *angina pectoris* or in those who have had myocardial infarctions in the past



are no different than with other heart lesions associated with failure. But with acute myocardial infarction the situation is different since both the drug and the disease favor precipitation of ventricular tachycardia and ventricular fibrillation. With mild degree of failure it is usually best to withhold digitalis since failure often disappears as the general condition of the patient improves. But with progressive failure or severe failure which is in itself endangering the patient's life, digitalis should be used. There is a definite risk connected with its use but it is not prohibitive and should be accepted just as one accepts the risk of using large doses of quinidine for ventricular tachycardia under the same circumstances. On theoretical grounds a ration of quinidine given along with digitalis should lessen the hazard of precipitating ventricular tachycardia, but I know of no data bearing on this point.

In heart failure with *hyperthyroidism* digitalis is indicated just as it is in heart failure associated with other types of lesions. In some patients with auricular fibrillation more than the average amount of digitalis is required to slow the ventricular rate, but as a rule the dose is within the expected range. It is of no use in slowing the rapid sinus rhythm of uncomplicated hyperthyroidism.

Discussions of the indications for the use of digitalis in heart failure complicating infections and surgical procedures are included mainly to emphasize the fact that shock and shocklike states which complicate these conditions are not heart failure and are not benefited by digitalis. However, these conditions are at times complicated by heart failure especially in older individuals and in those who have a chronic heart lesion. Under these circumstances digitalis should be used in the usual manner.

Christian<sup>11</sup> has advocated the use of digitalis in certain patients who may later develop heart failure for the purpose of preventing it. Although this proposal has merit there is little experimental or clinical evidence to support it, and the decision to use it for this purpose depends largely on the personal opinion of the physician.

**The Administration of Digitalis in Heart Failure**—One now has the choice of a wide variety of effective digitalis preparations. The newer preparations, usually pure glucosides from various sources, have a definite place in digitalis therapy but in most cases pills, compressed tablets or capsules made from the leaf should be used. These preparations retain their potency over long periods of time unless they become moist, and the size of the individual dose is uniform. The tincture may be unpleasant to take and deteriorates to some extent with age, but its main disadvantage is the difficulty in obtaining uniform dosage because of the variation in the size of drops. One rarely encounters difficulties due to variation in the strength of the drug and even if this should occur it can be recognized by the effects on the patient.

The purpose of digitalis therapy is to produce the optimum therapeutic effect within a short space of time and to maintain this effect



The requirements are seldom outside the range of 0.1 to 0.2 gm per day, although there are many patients at either extreme. All gradations of dosage can be conveniently obtained with 0.1 and 0.2 gm tablets. When the requirements are not met by a regular daily dose of 0.1 or 0.2 gm, a satisfactory ration may be obtained by giving a tablet every other day or five or six times weekly. Only a few patients require more than 0.2 gm daily, and marked sensitivity is rare.

It is usually simple to judge, with both the initial and maintenance doses, when the optimum therapeutic effects have been obtained. When there is auricular fibrillation the heart rate, not the pulse rate, is a simple and accurate guide. A resting heart rate of seventy to eighty beats per minute is desirable. With sinus rhythm one is guided by careful observation of the signs and symptoms of heart failure. If improvement is striking, with relief of dyspnea and orthopnea and disappearance of signs of congestion, the problem is simple. If improvement is less obvious it may be necessary to push the drug to the point of producing mild toxic effects, since there is often only a narrow margin between the effective therapeutic and toxic doses.

**Toxic Effects**—Of the toxic symptoms loss of appetite, nausea of a particularly disagreeable sort and vomiting are the most common. Diarrhea is less common and yellow vision is rare. Disturbances of rhythm make up the remaining toxic effects. Ventricular premature beats giving rise to bigeminal rhythm or occurring irregularly are common, but those present before digitalis is used often disappear afterward and do not contraindicate its use. Ventricular tachycardia, auricular tachycardia, often with auriculoventricular block, auricular fibrillation and flutter and auriculoventricular nodal rhythm sometimes occur. Various degrees of auriculoventricular block are not uncommon but sino-auricular block is rare. The most frequent arrhythmias, and in many cases the less common ones, can be recognized at the bedside. However, ventricular tachycardia, the most serious of all the toxic effects, may be difficult to recognize. It occurs almost exclusively with either gross overdosage or with the most severe degrees of cardiac damage. It may be suggested at once by a sudden increase in heart rate, but this effect is often obscured since many of these patients already have a rapid rate. It should be suspected, then, not only when there is a sudden increase in heart rate but when there is a gradual increase in rate or failure of the expected slowing of the heart after an adequate dose of digitalis. An electrocardiogram will reveal at once the curious alternating ventricular complexes characteristic of ventricular tachycardia due to digitalis. This plan will also insure the recognition of other arrhythmias due to toxic effects of the drug.

Except in the case of moderate lengthening of conduction, digitalis should be stopped when any of the toxic effects appear, but it need not be abandoned. It should be withheld until they are gone, then resumed in a smaller dose. When toxic effects occur with small amounts of the

drug, other preparations should be tried. Their use will be discussed later.

**Contraindications**—If the indications for the use of digitalis as outlined above and the rules regarding toxic effects have been observed, there is little more to say regarding contraindications. Digitalis is contraindicated in ventricular tachycardia and in the typical form of beriberi heart. It is said to be contraindicated in hypersensitive carotid sinus syndrome, but in this clinic it has been used in the treatment of heart failure in a number of such patients without inducing unfavorable effects. It is likely, however, that in some patients with this syndrome digitalis may aggravate the symptoms because of its effects on the vagus. It should, therefore, be used with caution.

**Duration of Treatment**—There is no general rule to guide one in determining how long digitalis should be given but in general, once it has been found to be effective in the treatment of heart failure, it should not be discontinued. It may be withdrawn in patients in whom the cause of the heart failure can be removed, such as those with Graves' disease or arteriovenous fistula. At times it may be withdrawn in patients in whom heart failure is precipitated by some factor which is not likely to be repeated, such as an acute infection or a temporary arrhythmia.

**Use of Pure Glucosides Having a Digitalis Action.**—In Europe various glucosides having a digitalis action have been widely used but in the United States interest in their use is comparatively recent. The ones most commonly used are *cedilanid* and *digoxin* obtained from *Digitalis lanata*, *urginin* obtained from squill and *strophanthin*. All are effective preparations and have a definite place in cardiac therapy. They have some advantage over powdered leaf since they are pure substances and the dose is determined by weight rather than by biological standardization, but if one considers the uniform strength of present day preparations of powdered leaf and the fact that the dose of any preparation must be determined by the effects on the individual patient, these advantages become largely theoretical. There may be other advantages. Moe and Visscher<sup>12</sup> showed in animals that *cedilanid* was less toxic in the sense that there was a wide margin between the effective therapeutic and toxic doses. Occasionally this effect appears to be demonstrated in man. Certain individuals who cannot be digitalized with powdered leaf because of the early appearance of toxic effects may at times be successfully treated with one of the pure glucosides. Many times the same toxic effects will appear but one succeeds often enough to warrant the systematic trial of pure glucosides in such patients.

**Parenteral Administration of Digitalis Glucosides.**—Digitalis glucosides are also useful when parenteral administration is indicated. Although the use of *strophanthin* for this purpose has been known for many years, it has never been widely used in this country perhaps because it was seldom available or was available only in a preparation of uncer-

tain strength. However, reliable preparations of cedilanid, digoxin, strophanthin and ouabain are now readily available and are to be preferred when intravenous administration is indicated.

Parenteral digitalis administration is indicated only in emergencies, in patients who cannot take the drug by mouth, and at times in arrhythmias.

In emergencies reference has always been made to the rapid effects of venesection and oxygen administration, but often facilities for instituting these measures are not immediately available. The administration of any of the pure glucosides is simple and they are rapidly effective, maximum effects occurring within from five minutes to two hours.

#### ORAL AND INTRAVENOUS DOSAGE OF COMMONLY USED CARDIAC GLUCOSIDES

Preparation	Digitalizing Dose		Daily Maintenance Dose (Oral)	Reference
	Oral	Intravenous		
Cedilanid	6.25 mg in 48 hrs 7.5 mg in 72 hrs	1.6 mg 1.2 mg followed by 0.4 mg every 3-4 hrs until digitalized	0.75-1.25 mg 0.5-2.5 mg, average 1.6 mg	Fahr and La Due <sup>13</sup> Sokolow and Chamberlain <sup>14</sup>
Digoxin	1.0-1.5 mg	0.75-1.0 mg	0.5 mg	Wayne <sup>15</sup>
G-Strophanthin (Ouabain)	0.5 mg			Batterman, Rose and DeGraff <sup>16</sup>
Urginin	6.5-14.0 mg in 72 hrs Average 9.0 mg		0.5-1.5 mg, average 0.95 mg	Chamberlain and Levy <sup>17</sup>

When the drug cannot be taken by mouth one has the choice of rectal administration of tincture or suppositories, and intravenous, intramuscular or subcutaneous administration of one of the pure glucosides. Digoxin is irritating and must be given by vein. Any of these methods is effective but the assurance that all of the drug will be available makes the intravenous route preferable. It may be poorly absorbed from muscle and subcutaneous tissues in edematous individuals and it is sometimes expelled when given by rectum. The pure glucosides, either with oral or intravenous use, are administered according to the same principles which govern the use of the crude drug and the same toxic effects may occur. Before any intravenous preparation is given one must be sure that the patient has not recently received digitalis or any preparation having digitalis effect.

The dosage for oral and intravenous use of the preparations is given in the table. In emergencies the full dose should be given at once but in other situations some physicians prefer to divide the initial therapeutic dose into two equal portions given at an interval of several hours.

#### USE OF DIGITALIS IN TREATING CARDIAC ARRHYTHMIAS

Digitalis has a definite place in the treatment of cardiac arrhythmias both for the purpose of preventing them and for terminating them. Its use in this field deserves more consideration than it has received in the past, and takes on added importance because of the dwindling supply of quinidine.

**Prevention of Paroxysmal Auricular Tachycardia**—The use of digitalis for the purpose of preventing attacks of paroxysmal auricular tachycardia is mentioned in some texts but only Levine<sup>18</sup> feels that it is superior to quinidine, and there is little information in the literature<sup>19</sup> suggesting its use. Paroxysmal auricular tachycardia is a common disorder but its course is so unpredictable that it is difficult to collect a group of records suitable for critical analysis of the effectiveness of digitalis or for comparing its effectiveness with that of quinidine. In this clinic when preventive treatment is indicated we prefer to try digitalis first, partly because we have the impression that it is at least as effective as quinidine and also because it has certain practical advantages over quinidine, particularly for a form of therapy which must often be indefinitely continued. Digitalis is cheaper, only one daily dose is required as compared with a minimum of three with quinidine, and if the daily dose is accidentally omitted there will be no appreciable reduction in the effective amount of digitalis while the effects of quinidine rapidly diminish. It is not always effective and one must remember that digitalis is contraindicated in ventricular tachycardia. If this is suspected digitalis should not be given unless there is electrocardiographic proof of the nature of arrhythmia.

The following brief case reports illustrate its effectiveness.

**CASE I.**—Mrs. D. P., aged 34 entered complaining of attacks of palpitation for four years occurring regularly before each menstrual period and accompanied by nausea, vomiting and emotional upsets. They occurred despite quinidine. Physical examination, x ray of the heart, electrocardiograms and basal metabolic rate showed nothing remarkable. No attacks were observed during a week's observation but the day after dismissal she returned because of an attack of twelve hours duration. The heart was regular at 200 beats per minute. There were no signs of heart failure and the attack was stopped after 2.2 gm of quinidine in twenty hours. Electrocardiograms during the paroxysm showed a regular rhythm with a rate of 200, no P waves, a QRS of 0.11 seconds and deeply inverted T waves in Leads II and III.

The patient was dismissed to take quinidine 0.2 gm three times daily but returned in one month because of a similar attack of three days' duration. The heart rate was again 200 and the electrocardiogram the same except for readily identifiable P waves preceding each ventricular complex. The paroxysm ended after 1.2 gm of quinidine in nine hours. She was digitalized and dismissed on a

maintenance dose of 0.1 gm of powdered leaf daily. No attacks occurred in the next three months.

**CASE II**—Mr F G., aged 65, came to the clinic because of attacks of palpitation accompanied by dizziness for three months. General physical examination and x-ray examination of the heart were not remarkable. Electrocardiogram showed the short PR, wide QRS syndrome. Further records on numerous occasions showed paroxysms of auricular tachycardia. These frequently consisted of short paroxysms which came on with inspiration and stopped during expiration. They could be completely abolished by tilting the patient to an angle of 65 degrees and made to reappear by tilting back to the horizontal position. On 45 drops of tincture of belladonna daily they appeared to become less frequent but were not abolished, but with a maintenance dose of digitalis of 0.2 gm daily they completely disappeared and could not be induced, on many tests over a period of three months, by deep inspiration or tilting back and forth between the vertical and horizontal.

**CASE III**—Miss D M., aged 50, was seen because of attacks of tachycardia occurring several times a week for the past few months. Physical examination showed nothing remarkable. An attack of tachycardia with a rapid regular rhythm of 180 was observed, which stopped with carotid sinus pressure. On a maintenance dose of 0.1 gm. of digitalis daily only a few attacks occurred in the next few months. These were brief and caused little inconvenience.

**Prevention of Paroxysmal Auricular Flutter and Fibrillation**—Digitalis is also useful as a preventive measure in the treatment of paroxysmal auricular flutter and fibrillation. Its use for this purpose has been objected to on the grounds that it might transform a paroxysmal arrhythmia into a permanent one, since digitalis sometimes induces arrhythmias. However, this is so uncommon that it does not constitute a serious contraindication. In some cases<sup>20</sup> digitalis clearly prevents attacks, in others it is beneficial even though paroxysms occur *since* the increase in ventricular rate with the paroxysm is modified or prevented by digitalis. Patients treated in this manner have reported little inconvenience from attacks when they have occurred, and on a few occasions attacks of paroxysmal auricular fibrillation have been observed in individuals at a time when, because of a slow ventricular rate, they were not aware of any change in heart rhythm. Gold<sup>21</sup> has stated that this does not occur, at least in individuals without heart failure, but we have not seen patients of this sort.

When digitalis is given for the purpose of preventing paroxysmal arrhythmias, it is best to give it by the method suggested previously for slow digitalization.

**Termination of Chronic Auricular Flutter**—Fahr and LaDue<sup>13</sup> have reported reversion to normal rhythm in a number of patients with chronic auricular fibrillation following intravenous cedilanid. One does not as a rule expect this to take place but digitalis is effective for this purpose in auricular flutter and in paroxysmal auricular tachycardia. Its action in auricular flutter is well known. The usual instructions are to digitalize the patient, often to the point of producing mild toxic symptoms, with the expectation that auricular flutter will be converted to auricular fibrillation. If this occurs, digitalis is withdrawn and,

if the treatment is successful, reversion to normal rhythm then takes place. Withdrawal of digitalis when auricular fibrillation occurs complicates the treatment since it is often difficult to distinguish between the two arrhythmias without frequent electrocardiograms, particularly after digitalis has been given. This step seems illogical and experience in this clinic has shown it to be unnecessary. The change from auricular fibrillation to sinus rhythm often occurs in too short an interval to have allowed time for a significant reduction of the amount of digitalis in the body. It may be necessary at times to reduce the dose of digitalis with the appearance of auricular fibrillation, since this may be accompanied by a considerable fall in ventricular rate. Otherwise the management of auricular flutter is the same as it is for auricular fibrillation. Enough digitalis is given to lower and maintain the ventricular rate at 70 to 80 beats per minute, and one is not obliged to determine from day to day whether or not auricular fibrillation has appeared. If this treatment fails to restore normal rhythm, the usual plan of giving quinidine is followed.

In this clinic twenty-four patients with chronic auricular flutter have been treated according to this plan. With digitalis alone, normal rhythm was restored in fourteen, or 57 per cent. Of the remaining patients, those in whom digitalis had failed, normal rhythm was restored with quinidine in four, two were left with chronic auricular fibrillation and four with chronic auricular flutter.

Anything which would shorten the treatment of auricular flutter would be welcome, since reversion to normal rhythm is seldom accomplished in less than a week. It is therefore of considerable interest that there are now on record a number of instances in which intravenous glucosides have brought about a rapid reversion to normal rhythm. Parkinson and Bedford<sup>22</sup> observed it in two patients after intravenous strophanthin. Using cedilanid by vein, Fahr and LaDue<sup>13</sup> reported reversion to normal rhythm in two patients within a few minutes and in a third patient within twenty-four hours. Sokolow and Chamberlain,<sup>14</sup> using the same preparation, noted reversion to normal rhythm in three patients within eighteen, thirty-six and forty-eight hours. Fahr and LaDue administered the full therapeutic dose at once while Sokolow and Chamberlain used a less rapid plan of administration. These reports should encourage further trial of intravenous glucosides for this condition with the hope that in at least some patients with auricular flutter the period of treatment can be shortened.

**Termination of Paroxysmal Auricular Tachycardia**—There is seldom urgent need of terminating attacks of paroxysmal auricular tachycardia since the attacks are usually self-limited. However, in prolonged attacks or attacks with an extremely rapid ventricular rate, serious heart failure may occur even with a normal heart. Quinidine is probably the drug of choice in this state but it is important to know that intravenous digitalis preparations may also be effective. Wilson and Wishart<sup>23</sup> first reported the successful use of intravenous digitalis for this



purpose, and Fahr and LaDue<sup>13</sup> report five cases successfully treated with intravenous cedilanid. Curiously enough, the largest body of evidence bearing on the effectiveness of digitalis in paroxysmal auricular tachycardia is contained in a report by Hubbard<sup>24</sup> concerning this condition in infants. Nine infants, five of them three weeks old or less, were successfully treated by intramuscular digifolin. The initial dose was 0.1 gm and the total amount given any patient was 0.3 gm. In some patients the total amount was given in three doses within twenty-four hours.

While there is not enough information to permit an adequate definition of the place of digitalis in the treatment of paroxysmal auricular tachycardia for the purpose of terminating the attack, it should be considered after quinidine has failed. It has an advantage over other preparations in patients with heart failure because of the general effect of digitalis on heart failure and because significant slowing may occur<sup>23</sup> even if the arrhythmia persists. It should not be given without electrocardiographic proof of the nature of the tachycardia.

#### BIBLIOGRAPHY

- 1 Eggleston, Cary. *Arch. Int. Med.*, 161, 1915
- 2 Gold, H. and Cattell, M. *Arch. Int. Med.*, 65, 263, 1940
- 3 Christian, H. A. *Am. J. Med. Sc.*, 157, 593, 1919
- 4 Marvin, H. M. *J. Clin. Investigation*, 3, 521, 1926
- 5 Luten, D. *Arch. Int. Med.*, 33, 251, 1924
- 6 Wood, P. *Brit. Heart J.*, 2, 132, 1940
- 7 Graybiel, A. and White, P. D. *Am. J. Med. Sc.*, 192, 334, 1936
- 8 Schwartz, S. P. *Am. Heart J.*, 4, 408, 1929
- 9 Blumgart, H. L. and Altschule, M. D. *Am. J. Med. Sc.*, 198, 455, 1939
- 10 Campbell, M. *Brit. Heart J.*, 4, 131, 1942
- 11 Christian, H. A. *J.A.M.A.*, 100, 789, 1933
- 12 Moe, G. K. and Visscher, M. B. *J. Pharmacol. & Exper. Therap.*, 64, 65, 1938
- 13 Fahr, G. and LaDue, J. *Am. Heart J.*, 21, 133, 1941
- 14 Sokolow, M. and Chamberlain, F. L. *Ann. Int. Med.*, 18, 204, 1943
- 15 Wayne, E. J. *Clin. Sci.*, 1, 63, 1933
- 16 Batterman, R. G., Rose, A. and DeGraff, A. C. *Am. Heart J.*, 20, 443, 1940
- 17 Chamberlain, F. L. and Levy, R. L. *Am. Heart J.*, 14, 268, 1937
- 18 Levine, S. A. *Clinical Heart Disease*, 2nd ed. Philadelphia, W. B. Saunders Co., 1940
- 19 Barrier, C. W. *Ann. Int. Med.*, 5, 829, 1932
- 20 Schwartz, S. P. *Am. Heart J.*, 6, 458, 1931
- 21 Gold, H. *J.A.M.A.*, 112, 322, 1939
- 22 Parkinson, J. and Bedford, D. E. *Quart. J. Med.*, 21, 21, 1927
- 23 Wilson, F. N. and Wishart, S. W. *Am. Heart J.*, 5, 549, 1930
- 24 Hubbard, J. P. *Am. J. Diseases Child.*, 61, 687, 1941

#### GENERAL REFERENCES

- Cushny, A. R. *Digitalis and Its Allies*. London, Longmans, Green & Co., 1925  
 Dock, W. *Digitalis Administration*. International Clinics, 3, 186, 1933  
 Luten, D. *The Clinical Use of Digitalis*. Springfield, Ill., Charles C. Thomas, 1936  
 Robinson, G. C. *The Therapeutic Use of Digitalis*. Baltimore, Williams & Wilkins Co., 1923

## CLINICAL RELATIONSHIPS BETWEEN ARTERIAL HYPERTENSION AND THE KIDNEYS

DAVID A. RYTAND, M.D.\*

ARTERIAL hypertension is only a sign of disease, not necessarily a disease in itself. Even though careful search of most hypertensive patients usually fails to disclose a reason for the abnormal pressure, it is still useful in protecting other patients from improper treatment, in the management of the hypertensive patient, and in arriving at a prognosis. During this search, it is not uncommon to discover proteinuria or other evidence of renal disease, the purposes of this paper are to discuss the diagnostic and therapeutic problems raised by the occurrence of a renal lesion in the hypertensive patient, and to review the pertinent basic concepts which have been so well summarized recently<sup>1, 2, 3</sup>

### ETIOLOGIC RELATIONSHIPS BETWEEN HYPERTENSION AND THE KIDNEYS

At least logically, there are three ways by which hypertension and the kidneys could be related: renal lesions might cause arterial hypertension, hypertension might result in renal disease, and still other disorders might simultaneously damage the kidneys and elevate the blood pressure. Unfortunately, the following separation of certain situations into these three categories is more certain in black and white than it is in actual patients.

**Renal Disease Causing Hypertension**—Many varieties of bilateral primary disorders of the kidneys result in hypertension, especially when renal failure (uremia) is present; among others, these include glomerular nephritis in early and late stages, polycystic disease, pyelonephritis, and obstruction of the urinary tract. Patients with periarteritis nodosa, disseminated lupus or related syndromes are usually hypertensive only with associated renal failure: their arterial pressures are normal either when the kidneys are not involved or when renal tubular degeneration predominates.<sup>4</sup> These syndromes therefore seem to behave as glomerular nephritis in relation to hypertensive effect.

The mechanism by which renal disease elevates arterial pressure is not established, nor has it been thoroughly studied. Diffuse renal lesions have been compared without adequate basis, to experiments in which the pressure is raised by partial occlusion of the renal artery, it has been claimed that renal ischemia is responsible for hypertension in both. Although the perfusibility of the kidneys removed at necropsy

From the Department of Medicine, Stanford University School of Medicine, San Francisco, California.

\* Assistant Professor of Medicine, Stanford University School of Medicine.

is very low when renal damage has caused death in uremia,<sup>5</sup> indirect estimations of renal blood flow during life in patients with glomerular nephritis seem to indicate hyperemia.<sup>3</sup> In rats made hypertensive with a diffuse renal lesion after subtotal nephrectomy, blood flows through the abnormal remnant of kidney at a normal rate.<sup>6</sup>

On the other hand, the rate of renal blood flow is surprisingly low in subjects with coarctation of the aorta,<sup>7</sup> in whom the kidneys are apparently normal otherwise, it has been suggested that the arterial hypertension with this anomaly represents the clinical counterpart of the Goldblatt type of experiment. Experimental studies on this variety of hypertension, caused by partial occlusion of a renal artery, show that it persists after denervation by transplanting the kidney,<sup>8</sup> thereby involving a humoral substance. Whether this constricts arterioles by peripheral action or via the central nervous system<sup>9</sup> is not certain, and its relation to the renin-angiotonin series is not established.

Recent attempts have not yet succeeded in naming the juxtaglomerular apparatus as the precise source, within the kidney, of renal hypertension.<sup>3</sup>

In the last few years attention has been directed to unilateral renal lesions, usually atrophic pyelonephritis, as a cause of hypertension, since such lesions are removable they might be of more practical importance than bilateral ones. Unfortunately, arterial hypertension is rarely associated with lesions of this type and is even less often relieved by nephrectomy,<sup>1, 10</sup> we have seen only two successful results in this clinic.

Complete removal of both kidneys causes little or no increase in arterial pressure experimentally. Clinically, hypertension is rare in acute anuria and is uncommon in some varieties of chronic renal disease, these include the "surgical" types of renal lesions, the nephrotic stage of glomerular nephritis, amyloidosis, and the lesions with multiple myeloma and subacute bacterial endocarditis (even with uremia). There is no satisfactory explanation for the usual failure of these lesions to elevate arterial pressure.

**Essential Hypertension**—High blood pressure follows gross renal disease in only a small proportion of all hypertensive patients, and is even more rarely associated with other etiologic factors such as a tumor of the adrenal medulla. In the great majority of cases, careful search fails to reveal a reason for the elevated diastolic pressure level, in these patients it may then be said that essential hypertension is present.

Now it is obvious that there must be some underlying reason for the generalized arteriolar constriction which is manifest clinically as hypertension, the renal factor was partially discussed above. It may now be added that essential hypertension is regarded by some to be of renal origin, although this view is becoming less popular as the evidence for it grows more complex.<sup>1, 2</sup>

Although an obscure metabolic fault in the kidneys<sup>2</sup> may eventually

become established as the cause of essential hypertension, simple renal ischemia increasingly seems less likely to be involved. The arteriolar lesions found in the kidneys at necropsy are usually absent earlier in the disease,<sup>11</sup> and even after death renal perfusibility is not often decreased in the absence of uremia.<sup>6</sup> Clinicians have long been impressed by the "nervous" element in patients with essential hypertension, studies have newly emphasized the fact that organic disease of the central nervous system in man and experimental interference with the nervous system in animals may be followed by an elevation of arterial pressure. A neurogenic element has been implicated even with renal hypertension.<sup>9</sup>

**Hypertension Causing Renal Disease.**—The concept that essential hypertension had its origin in renal ischemia arose, at least in part, from the fact that vascular changes are associated with hypertension of any cause, and are often prominent in the renal vessels.

These changes are of two kinds, corresponding roughly to the size of the involved vessels. First, renal arterioles presumably participate in the generalized systemic arteriolar constriction which causes hypertension, as well as in the medial hypertrophy which is an early sequel. Secondly, increased arterial pressure initiates or accelerates atherosclerosis, it is chiefly this alteration in the larger arteries which complicates the course of the hypertensive patient, as by occluding cerebral or coronary arteries.

Renal arterial pressure remains normal distal to the partially constricted artery responsible for hypertension in the rest of the experimental animal, under these conditions, vessels in the kidney are protected from the changes occurring elsewhere.<sup>12</sup> In essential hypertension there is no such protection and therefore renal arteriosclerosis accompanies cerebral, retinal and cardiac arteriosclerosis.

This event may add a renal factor to hypertension which arose elsewhere, and produces abnormal results when renal blood flow and other functions are measured by modern methods.<sup>1, 2</sup> It is of more practical importance to recognize that renal arteriosclerosis, while not often causing death in uremia, is the lesion responsible for the abnormal urine of most hypertensive patients.

Anatomic changes in the shrinking kidneys are evident in the urine in the form of moderate amounts of protein, with a few casts, erythrocytes, leukocytes and renal tubular cells in the sediment. If heart failure supervenes, the urinary abnormalities increase in degree with renal congestion. Gross hematuria may accompany the malignant stage of essential hypertension with arteriolar medial necrosis, or may appear as part of uremia's purpura. As function decreases, urine becomes dilute and its specific gravity less variable. Rough tests of the blood show retention of metabolites.

**Hypertension and Renal Lesions Associated with a Third Factor.**—More than a few uncertainties were noted above, we know even less about

states in which the blood pressure and kidneys are involved more or less at the same time in the presence of a third process. One could, of course, include the periarteritis nodosa group and even acute glomerular nephritis in this section, but two other illustrations may be better.

The first of these is that of *intercapillary glomerulosclerosis*, a renal lesion usually found only in middle-aged patients with diabetes mellitus, and then especially together with a syndrome of arterial hypertension, marked proteinuria and abnormal urinary sediment, edema due chiefly to hypoproteinemia, and renal failure.<sup>13</sup> The diabetes almost always comes first, and is mild. Microscopic lesions may be of severe degree without the complete syndrome, and the causal relationships are not yet clear. The syndrome is of particular interest because it is uncommon for hypertension to exist with edema caused by low concentration of the serum protein and with intense renal tubular degeneration and proteinuria (the nephrotic syndrome).

This unusual combination is even more striking in *eclampsia toxemia* (pre-eclampsia), no longer thought to be the result of disturbed renal function.<sup>14</sup> Here again one finds a third factor, an abnormal state during pregnancy, associated in unknown ways with hypertension and a degenerative renal lesion, and with edema often a consequence of hypoproteinemia. Unlike the syndrome in the previous paragraph, renal failure is rare in pre-eclampsia. Prolonged toxemia is often followed by persistent hypertension.

Pre-eclampsia occurring late in pregnancy is to be distinguished from those situations in which the course of previously existing hypertension or renal disease is complicated by the occurrence of pregnancy. Under these conditions the original disorder may remain relatively unchanged, but usually becomes worse comparatively early. After termination of pregnancy, the underlying condition may be little or no more severe than before. Pre-existing hypertension is much more apt to cause trouble than a previous renal lesion with normal pressure and function.

#### GUIDES TO DIFFERENTIAL DIAGNOSIS

With the above material as background, the significance of family and personal histories, physical examination and laboratory studies may now be discussed.

**Family History**—The patient with essential hypertension may tell of a high incidence of hypertensive disease or its sequels in his family history. So may the one who has polycystic kidneys, although he is apt to speak of kidney trouble "High blood pressure" as a cause of death in aged relatives may usually be ignored, as an elevation of systolic pressure with normal diastolic pressure is common with arteriosclerosis, the latter, not hypertension, may also have been responsible for cardiac and cerebral manifestations.

**Personal History**—The recent "present illness" part of the story is apt to consist of shortness of breath, fatigue or other complications

of hypertension, it must be carefully heard for its clues to proper management of the patient. More rarely the complicated illness suggests a syndrome in the periarteritis nodosa group as the patient tells of asthma, joint troubles and a rash, the aging gentleman's difficulty in emptying his obstructed bladder may be important, abdominal pain in another leads to the discovery of polycystic kidneys, the presence of advanced pregnancy scarcely needs telling.

The past personal history is more useful in evaluating the significance of renal disorders accompanying hypertension. In earlier examinations (for life insurance, pre-employment, military service, and so forth), was high blood pressure found before or after albumin in the urine? Had the patient had trouble, or the physician betrayed alarm toward the end of pregnancy? Was a bad sore throat followed shortly by the puffy eyelids or smoky urine of acute glomerular nephritis? Had there been a period of painful burning or frequent urination, or chills with fever and backache, as the early events of urinary tract infection which has become chronic pyelonephritis? Was there ever an operation on or about or below a kidney as a possible cause of unilateral renal disease? Was the urine ever bloody possibly at a time when there was severe colicky pain of a stone? Such specific questions help in deciding whether a renal lesion found with hypertension plays an etiologic role or is merely a complication.

**Physical Examination**—The physical examination also serves two purposes, first in evaluating the damage done by hypertensive disease and secondly in seeking a reason for hypertension. As to the latter, simple inspection reveals the typical facial erythema with disseminated lupus, polycystic kidneys are found on palpation, dilated intercostal arteries and delayed, small or absent femoral pulses indicate coarctation (with which hypertensive retinopathy is strangely uncommon). Since these are so rarely found, examination is most helpful in finding what harm has been done by elevated pressure in the way of vascular changes, particularly one notes any signs of cerebral arteriosclerosis, looks for retinal damage, and searches for the cardiac enlargement, gallop, basal rales or systemic congestion of heart failure. These, more than the mere level of arterial pressure, determine the prognosis and guide management of the patient.

**Laboratory Studies**—There are only three really important laboratory aids for an understanding of most patients with renal disease and hypertension: these are careful examination of the urine, a simple test of renal function, and pyelograms by intravenous injection of a contrast medium if renal function seems normal.

To be sure, other methods of study are indicated in a very few patients. It may be helpful to find an elevated concentration of serum globulin when one of the periarteritis group is suspected, or to confirm that suspicion by muscle biopsy, a roentgenogram may reveal the notched ribs and absent aortic knob typical of coarctation. Still

other laboratory studies may be useful in assessing what damage hypertensive disease has done. The radiologist's finding of cardiac enlargement and pulmonary congestion will often confirm the results of physical examination or the patient's story of breathlessness. The electrocardiogram is apt to be misleading, except for characteristic changes of myocardial infarction, because of the high incidence of abnormal T waves with left ventricular preponderance.

The *urine* may be apparently normal not only when renal disease is absent, but also in two situations in which renal lesions play a part in elevating arterial pressure. First, with complete obstruction of a ureter the abnormal side contributes nothing at all to the urine, secondly, healed or atrophic pyelonephritis may similarly alter blood pressure with little or no urinary evidence of its presence. One must also remember that hyaline casts and erythrocytes are dissolved in alkaline urine, particularly if dilute, and that it is more difficult to detect small amounts of protein in dilute urine. Concentration tests are best used not as tests of renal function but as a means of obtaining concentrated urine suitable for examination, this should include the method of Addis<sup>15</sup>

Erythrocytes and especially leukocytes in the sediment, with small degrees of proteinuria, suggest pyelonephritis. This is sometimes erroneously diagnosed when glomerular nephritis is present, an error caused by misinterpretation of the latter's renal tubule epithelial cells as "pus cells." Casts (hyaline, granular or epithelial) do not mean glomerular nephritis, but occur with any diffuse renal lesion. It is obvious that urinary tract infections are commonly found as complications of hypertension, they cause it much less often.

Early in glomerular nephritis the predominance of blood casts and erythrocytes over leukocytes and tubule cells simplifies the diagnosis. Later, blood casts may be found only after long search. In the nephrotic stage such evidence of glomerulitis is usually lacking, the urine is full of protein, hyaline casts with fat droplets, and renal tubule cells packed with fat (oval fat bodies), similar findings occur in other nephrotic syndromes. Later in glomerular nephritis, the renal lesion as judged by urinalyses seems less intense, there are moderate and roughly proportional excesses of protein, erythrocytes, leukocytes and renal epithelial cells, and granular or epithelial casts. With the dilute urine of advanced renal disease hyaline casts are rare, but broad casts appear, the latter are found with renal failure of many causes. Both the urine and clinical features of late glomerular nephritis are indistinguishable from those of renal arteriosclerosis following essential hypertension. The presence of blood casts, fatty cells or casts, and broad casts all at once is highly suggestive of one of the periarteritis nodosa syndromes.<sup>4</sup>

*Tests of renal function* need not be complicated. The main question is whether renal disease is confined to one kidney or has involved both, the latter is established by finding an elevation of the blood

urea<sup>16</sup> or creatinine concentration above normal upper limits (generously 50 mg and 2 mg per 100 cc respectively) Some clinical laboratories seem able to measure blood urea-nitrogen (25 mg per 100 cc.) or total nonprotein nitrogen (50 mg per 100 cc.) more accurately than urea Creatinine is less subject than other substances with non-protein nitrogen to extrarenal sources of elevated concentration, urea, for example, may be increased in the blood in the absence of any renal disease. Otherwise, nothing is gained by measuring more than one of these substances, and very little useful information is added by determinations of dye excretion or clearances

*Intravenous pyelography* will rarely be either successful or helpful when simple tests show reduction of renal function, then measurement of residual urine volume in men and stereoscopic roentgenograms of the kidney region (for renal size or stones) are in order Intravenous pyelograms of the hypertensive patient are made either in the seeming absence of a renal lesion (normal urine) or in the presence of urinary abnormalities without reduced renal function, in an effort to uncover the rare instances of hypertension caused by renal disease amenable to specific treatment, this really means a unilateral abnormality

#### RENAL DISEASE AND THE TREATMENT OF HYPERTENSION

Enthusiasm aroused by apparent discovery of such a cause must be tempered before advising nephrectomy Minor deviations from perfectly normal pyelograms are common, and apart from the operative risk it is sometimes harmful to remove a kidney which appears to be functionless,<sup>10</sup> even in apparently well selected patients unilateral nephrectomy seems to be successful in curing hypertension in only one case out of ten<sup>1 10</sup>

*Atrophic pyelonephritis*, with a small and functionless kidney on intravenous pyelography, is the lesion most frequently found when good results follow nephrectomy Precise indications for the latter are not yet established. Of two successful cases in this clinic,<sup>17</sup> repeated pyelography in one showed unilateral loss of function but the removed kidney appeared almost normal, in the other, a previous renal operation had led to diffuse lesions in a kidney which nevertheless was able to concentrate the contrast medium

Having found a suspicious appearance, intravenous pyelography should be repeated If the lesion is still present, cystoscopy is necessary, not only for further exploration of the abnormal side but to obtain urine from, and assure the normal function of, the other side. Complete normality of the opposite kidney will not guarantee success on nephrectomy but abnormalities there cast grave doubt on the advisability of operation

The *pre-eclamptic toxæmia of pregnancy*, when mild, may be controlled by management which stresses rest and sedatives, with a diet



providing an adequate amount of protein while restricting sodium, diuretics are sometimes necessary. Unfortunately, prolonged toxemia is frequently followed by a form of hypertension which apparently is not distinguishable from essential hypertension, this does not so often come after severe toxemia, which is not allowed to be present very long. Since fetal mortality in toxemia is lower when labor is induced a month before term, such interference seems best for both mother and child when toxemia persists in spite of modern management.

But for the removal of a fetus from the pregnant uterus or the rare attack on a unilateral renal lesion, the conditions reviewed above are not often subject to specific therapy. Yet the presence of kidney disease alters treatment of the hypertensive patient in various ways.

Sulfonamides will frequently be given to patients with *urinary tract infections*, with impaired renal function more than the usual precautions should be taken. We are not convinced of their reported beneficial action in glomerular nephritis, but the latter does not contraindicate their use when necessary. Those who use thiocyanate in hypertension should avoid it when renal lesions are present.

The management of *congestive heart failure* in hypertension is made more difficult by the presence of true uremia (not including the relatively slight reduction of function in the congested kidney). Mercurial and even other diuretics may then not be used safely, digitalis and related glucosides more likely produce vomiting, and the associated anemia necessitates more thought before phlebotomy. One often desires to replenish the sodium and water stores of the uremic patient who is dehydrated, this must be done cautiously in the presence of hypertension, even when heart failure is not obvious, in order to avoid pulmonary edema.

While dietary reduction of urinary nitrogen excretion is not useful in hypertension without renal involvement, there is every reason to believe it reduces renal work and is therefore indicated when bilateral kidney damage is present<sup>18</sup> in an effort to minimize progression of the lesion. Urinary nitrogen is best reduced by a diet which first supplies an adequate number of calories and which daily gives about 0.5 gm of protein per kilogram of body weight, to the latter must be added an amount of protein equal to its daily loss in the urine. Dietetic details, including the need of vitamin and mineral supplements, must be decided in each individual case.

Finally, when section of the splanchnic nerves is contemplated, the presence of a renal lesion requires further consideration. The chances of a successful result are worst in those hypertensive patients who most need help, those with renal damage in the malignant phase of essential hypertension. On the other hand, nerve-cutting operations have succeeded in lowering arterial pressure at least temporarily in patients whose primary trouble was glomerular nephritis, that disease does not

contraindicate operation, no matter how bad the urine appears, if uremia is absent and hypertension dominates the clinical picture

## BIBLIOGRAPHY

- 1 Goldring W and Chasis, M. The Commonwealth Fund New York, 1944
- 2 Smith, H W. J Mt. Sinai Hosp., 10 59 (May-June) 1943
- 3 Bradley S E. New England J Med., 231 421-426 452-458 (Sept. 21 and 28) 1944
- 4 Krupp M., Arch Int Med., 71 54-61 (Jan.) 1943
- 5 Cox, A. J., Jr and Dock, W. J Exper Med., 74 167-175 (Sept.) 1941
- 6 Dock, W and Rytand, D A. Proc. Soc. Exper Biol. & Med., 36 196-198 (March) 1937
- 7 Friedman, M., Selzer, A. and Rosenblom, H. J Clin Investigation, 20 107-111 (March) 1941
- 8 Blalock, A. and Levy S E. Ann Surg., 106 826-847 (Nov) 1937
- 9 Dock, W., Shidler F and Moy B. Am. Heart J., 25 513-521 (April) 1942
- 10 Sensenbach W., Arch Int Med., 73 123-130 (Feb) 1944
- 11 Castleman, B and Southwick, R. H. J.A.M.A., 121 1256-1261 (April 17) 1943
- 12 Wilson, C. and Pickering, G W. Clin Sc., 3 343-355 (Aug) 1938
- 13 Siegal S. and Allen, A. C. Am J Med. Sc., 201 516-528 (April) 1941
- 14 Rytand D A. Stanford M Bull., 1 203-208 (Nov) 1943
- 15 Addis, T. J.A.M.A., 85 163-167 (July 18) 1925
- 16 MacKay E. M and Rytand D A. Arch. Int. Med., 55 131-140 (Jan.) 1935
- 17 Wallace, C. J. To be published Stanford M Bull., 1945
- 18 Addis, T. J Urol., 41 126-136 (Feb) 1939

# MODERN METHODS USED IN FINDING PULMONARY TUBERCULOSIS AND TREATMENT OF THE ASYMPTOMATIC CASE

PHILIP H. PIERSON, M.D., F.A.C.P.\*

It is of interest to note the progress that has been made in the program for finding cases of tuberculosis, especially since the founding of the National Tuberculosis Association and the American Trudeau Society. Their object has been the education of the public and the practitioner of medicine to the presence of this disease, methods of finding it, and its control through isolation and scientific treatment. Reporting of the disease, availability for sputum examinations, care of the undernourished child who was thought to be tuberculous, following up of the contacts of known cases, tuberculin testing of children and part of the adult population, with x-rays of the reactors, have been steps in this forward march. But still all too many cases were first discovered in a moderately or far advanced stage of their disease. This was at least in part due to the fact that patients and physicians waited for the classical symptoms of tuberculosis before taking sufficient steps to establish the diagnosis. Physical signs were relied upon until recent years and were pitifully absent even in moderately advanced disease. With the development of rapid strides in x-ray technic and interpretation, it was found that tuberculous and nontuberculous disease, including cancer and heart disease, could be suspected long before symptoms were experienced by the patient.

## RAPID SCREENING METHODS—HISTORICAL DATA

One of the first mass surveys with the fluoroscope was conducted at the University of Munich in 1927, when 5707 students were examined. During 1930, 3000 students at the University of Lwow were examined by the fluoroscope or x-ray films and since then it has become compulsory for all entering students. Photographing the fluoroscopic image dates back to 1895, less than six months after Roentgen discovered the x-ray, when Blever in England developed a technic for this procedure. In 1911, Caldwell in this country "clearly demonstrated that the camera recorded much more than the eye could see on the fluorescent screen." It was de Abreu of Brazil "who deserves the credit for putting

---

From the Department of Medicine, Stanford University School of Medicine, San Francisco, California

\* Clinical Professor of Medicine, Stanford University School of Medicine, Chief, Department of Tuberculosis, Stanford Clinic and Stanford Service, San Francisco Hospital

this method on a firm basis for mass thoracic survey work." Since 1936 he has used this method in mass surveys in Brazil, Argentina, Chile, Uruguay and several European countries. Lindberg and Hursh in this country received their stimulation in this work from de Abreu.

Is it any wonder then that even before the outbreak of World War II a great many groups of our population were being x-rayed on photo-fluorographic films. Along with these small films, sensitized paper films 14 by 17 inches were perfected and they were manufactured in rolls thus making developing and storage simpler and more economical than the celluloid films of the same size. They have been used perhaps most extensively by Edwards and his co-workers in New York City. Of the photofluorographic films there are two sizes, the 4 by 5 inch single or 4 by 10 inch stereoscopic films and the 35 mm films which are manufactured in rolls. The object of all these methods, which supplemented the regular 14 by 17 inch celluloid films, was low cost per exposure, ease and speed of developing and interpreting, economical storage and a reasonably good picture which would show significant disease.

#### INTERPRETATION AND ACCURACY

Naturally, it takes some time by even skilled observers to acquire proficiency in the art of interpreting these small films as it likewise does in the correct reading of the fluoroscopic image and 14 by 17 inch celluloid films of the lungs and heart. The fluoroscopic films are taken at a distance of 36 inches, one-half the distance used in taking regular sized films, and allowance must be made for magnification of the heart shadow and the granular appearance of small films when enlarged for reading. It is only to be expected that those who have perfected themselves by experience in the use of one type of film will become more adept in that method and prejudiced in its favor.

The interpretation of these paper 4 by 5 inch and 35 mm films then, must be done by those with experience and not by the individual who only occasionally reads regular x-rays of the chest. Considerable discredit can be cast on this method unless these precautions are carefully followed. Because of the simplicity in technic of these new procedures it has been possible to take about 200 pictures per hour (60 to 100 films per hour is a more reasonable goal). With the fluoroscope considerable speed can be developed in screening a large number of persons but after an hour or two of this rapid work the eyes of the operator become fatigued and he must rest in order to continue to do good work.

From all this it can be seen that our approach to tuberculosis has made significant progress for now we are able to x-ray large groups of apparently healthy individuals in a short period of time, at a cost which is not prohibitive and with pictures which correlate very well

with the standard films \* Douglass, Birkelo, Harmon and Vaughn in 1940 estimated that the accuracy of 4 by 5 inch films compared with 14 by 17 inch standard films was 97.4 per cent, and Bridge put the figure at 98.5 per cent. Spellman, in the same year, estimated that 35 mm films were about 90 per cent accurate. There is so much difference of opinion by observers reading 14 by 17 inch films that a true comparison of accuracy of different methods is impossible at the present time. In all these methods it is necessary to remember that we are dealing only with a screening method and that whenever there is a question of disease a standard film should be taken to verify the condition. In surveys it has been found that between 2 and 5 per cent of the persons must be checked in this manner.

In the order of their accuracy it has been quite generally agreed that we should put, first, stereoscopic 14 by 17 inch celluloid film, second, single 14 by 17 inch celluloid film, third, 4 by 5 inch stereoscopic or 14 by 17 inch paper film, fourth, 35 mm films, and fifth, the fluoroscopic study. The last is in this position possibly because of the inability for the eye to register all that the camera does and because there is no permanent record but it has the advantage in the hands of skilled observers of viewing the chest in many angles, thereby seeing behind the ribs and mediastinum, viewing the different chambers of the heart and seeing the motion of the diaphragm. Small faint infiltrates are sometimes missed. Its ease of use and lack of expense, however, offer much in its favor for the experienced man in his private practice.

#### COST DATA

The cost of taking paper 14 by 17 inch films, 4 by 5 inch and 35 mm celluloid films has been estimated as follows (figures probably do not include the equipment)

*Paper films* Mercer in 1941 stated that the cost was 25 cents per man x-rayed.

*Four by 5 inch stereoscopic films* Long in 1941 stated that their cost averaged 54 cents per man x-rayed and 63 dollars per case of tuberculosis found.

*Thirty-five mm films* Mercer stated in 1941 that the cost was 1 cent per man. Perhaps some of these figures do not include the cost of assembling people and filing the films.

*Miniature films* (size not stated) Galbraith stated in 1941 that the cost per recruit examined was 5 or 6 pence and that this covered the retakes on 14 by 17 inch standard film, plus the cost of processing, wages of staff and salaries of specialists.

*Fluoroscopic examination* Von Allman in 1942 stated that the cost per person fluoroscoped was 42 cents, the cost of each person needing

\* A conservative estimate of the number x-rayed by miniature films in the armed forces from 1942 to 1944 was 16,000,000, and by the United States Public Health Service, particularly in war industries, was 2,000,000 in the same period.

medical care was \$31 16 and the cost of each active case of tuberculosis discovered was \$87 71

#### POSSIBILITIES OF THE MASS SURVEY IN THE FIELD OF TUBERCULOSIS AND OTHER PULMONARY AND CARDIAC DISEASES

**Value of a Method for Determining Mass Morbidity**—Whether in times of peace or war it is essential that the health of every man, woman and child be kept at the highest level possible. According to Miller, 31 per cent of the second million called in the draft were unfit for general military purposes and 24 per cent of these were so because of tuberculosis. This group is a representative cross section of the male population between the ages of 21 and 36. The average of many other sets of figures places the percentage of significant tuberculosis as between 1.5 and 2 per cent, with one half of the victims in an active stage, unaware that they had the disease. Edwards in New York City, who surveyed a large group of apparently healthy persons, found rates varying from about 2 to as high as 8 per cent, with one half of them active. Large groups of industrial workers have essentially the same status. We have known for a long time that sickness varies inversely with the economic status. The National Health Survey in 1935-1936 stated that, of the first 2,308,600 persons in this group of urban dwellers, disabling illness of those on relief was 47 per cent higher for acute illnesses, and 87 per cent higher for chronic illnesses than the corresponding rates for families with incomes of \$3,000 and over. There are racial groups in which hereditary lack of resistance, crowded living conditions and low economic status have produced a particular high rate of tuberculous disease.

Now that the mortality rate as a whole has dropped from about 200 in 1900 to 41 per 100,000 in 1943, we have in this x-ray method the opportunity to search out the apparently well persons who have x-ray evidence of tuberculosis, from whose ranks the future deaths from this disease will come. It is possible to survey industrial plants where it is known that the mortality from tuberculosis among unskilled workers is two and one half times greater than among skilled workers and where the morbidity from this disease causes a large number of lost hours from work, and most important allows the victim with the active lesion to infect many of his fellow workmen. It also presents the opportunity of finding patients with minimal infection, so that with proper treatment they may be restored to health and working efficiency. There are many causes for the development of tuberculosis, such as physiological background, nutrition, housing and others, that still must be ferreted out, but the discovery of the early and especially the moderately advanced case will go a long way toward hastening the disappearance of tuberculosis.

**Industrial and Insurance Experience**—One of the first mass surveys in

this country was that conducted in the small industrial city of Framingham, Massachusetts in 1920-1923. It was found that for every death there were nine active cases and nine arrested cases. This has served as a guide for estimating morbidity. Mortality statistics are quite accurate but, since morbidity rates are dependent upon the reporting of the disease, more definite figures are needed than those of the Framingham study. In 1934 a mass x-ray survey was started in New York City and 400,000 persons were studied. An interesting and instructive comparison of the incidence of disease in the white and colored groups was made. In 1938 the mortality rate was 255 per 100,000 among the Negroes and 41 per 100,000 among the whites. In the Negroes between 15 and 20 years of age, the mortality rate was ten to fifteen times that of the same age white population, yet the morbidity was only two to three times as great, representing a higher case mortality among the Negroes. In individuals over 20, while the death rate among the colored group was three to ten times that of the whites, there were fewer cases of tuberculosis found among the Negroes than the whites, again pointing to a very high case mortality.

Other surveys such as those in the Army, in industrial plants and among pension holders, showed fewer cases of tuberculosis were found among Negroes over 26 years of age. In the New York survey, of 400,000 persons 8731 who had negative x-ray films were re-x-rayed fourteen months later and it was found that the yearly incidence rate was 2.4 annually. This, broken down, showed that the incidence among the whites was 1.3, the Negroes 2.8 and the Puerto Ricans 6.6 per 1000. By checking other sources on about 4000 who did not report for re-x-rays, the annual incidence was found to coincide quite closely—2.2 per 1000.

The Metropolitan Life Insurance Company figures showed an annual incidence of between 2.23 and 2.69 in their employees, in the Army it is 2.1 for whites and 2.56 for Negroes, and in steel workers it was 2.1. Hence, the annual incidence of the disease is determined by the number of persons in a community who serve as a focus of infection. The conclusion is obvious that the morbidity rate is not determined by mortality alone but by the resultant of mortality and annual incidence. The annual incidence among Metropolitan Life Insurance Company employees was 4 per 1000 in 1930, but this figure had been reduced to 0.7 per 1000 in 1941.

These figures on the annual incidence of tuberculosis are presented to show the part played in such a study by mass x-ray methods and also to point out ways which must be found to protect people from tuberculosis.

Sometimes it may be difficult to educate management of industry as to the value of a survey of all their employees. It not only saves lives but it saves money. Sparks reports the survey of 100,000 employees and their relatives over a seven year period. Recognition of

tuberculosis resulted in a decrease in the number of days of sick leave from this cause alone of 71 per cent and the saving of a large sum of money

**Use of the Mass Survey in General Hospitals and Prenatal Clinics.**—Another use of mass x-ray surveys is in general hospitals. Only to mention two studies, that at the University of Michigan by Hodges, and the one in Chicago by Tucker and Babcock, is most instructive. In the former, every patient admitted to the hospital was x-rayed, using the 35 mm film. Of approximately 100,000 films made, 70 per cent showed normal findings, insignificant findings were present in 20 per cent, and significant disease was shown in 10 per cent. Very shortly, Dr Hodges will publish a further breakdown of these figures

At the University of Chicago Clinic, largely a white population, everyone entering the Out-patient Department, about 15,000, was fluoroscoped. It was found that 4.1 per cent of those examined had reinfection tuberculosis, 1.43 per cent being active cases and 2.74 per cent inactive cases. At the Provident Hospital, Chicago, a Negro institution, 25,000 patients were fluoroscoped, 4 per cent were found to have reinfection tuberculosis, of which 2.6 per cent were active cases. These patients, of course, represent a group of people who are sick, but their complaints were surgical and medical and an effort was made to exclude those who knew they had tuberculosis. The above figures are quite striking and serve two purposes: (1) they suggest that the bizarre symptoms usually present in these cases might be reflex phenomena resulting from the latent or active tuberculosis, and (2) they lead to an early suspicion of tuberculosis. The latter is significant because a study of the lungs might normally be delayed several days (an average of 15.5 days in the medical wards of another large county hospital service). When it was known that the patient had pulmonary tuberculosis proper therapy was started at once, often saving the patient immediate operation. Suspicion of the presence of tuberculosis prompted immediate isolation so that other patients, nurses and interns were protected. Until this procedure of routine entrance x-rays was installed at the University of Michigan there was a higher incidence of primary tuberculosis among the nurses working in the general hospital than during their training on the tuberculosis wards where strict precautions were routine.

Mass surveys of the nurses and interns themselves have contributed materially to the finding of cases at a very early period, thus reducing materially the incidence of active disease.

Mass x-ray surveys have also been made in prenatal clinics. Dr. Ianne was a leader in this and found in 1939 by tuberculin testing and x-raying all reactors that 1.7 per cent of the reactors (41 per cent) showed clinically active tuberculosis at a time which was most crucial for the mother and the unborn child. By proper treatment there was no spread of the disease during or after pregnancy.



**Summary**—We have a screening method in the x-ray, be it standard sized or miniature films or fluoroscope, which will lead to the suspicion, at least, of tuberculosis in a large cross section of our population. When found by this method more than 50 per cent of the cases are minimal and generally respond promptly to proper therapy. Knowing that between 0.5 and 2 per cent of our population has active tuberculosis without symptoms should so intrigue our medical profession that fluoroscopy will be carried out or x-ray films will be taken routinely. The physician should make his own office a unit for mass surveys.

I have not mentioned the x-ray study of all the contacts of known cases of tuberculosis. This should never be neglected, for many cases of the disease are found in the immediate environment of the known case, they may represent the source of this case or the result of infection from it.

#### THE TREATMENT OF THE ASYMPTOMATIC CASE

As has been stated in the foregoing paragraphs, mass x-ray surveys are a screen. Not everyone who has a shadow in his miniature x-ray film has tuberculosis. A study of each case must be undertaken at once to establish the diagnosis definitely. First a 14 by 17 inch x-ray film (preferably stereoscopic) should be made. This may show that the original suspicion was erroneous and that no disease is evident, or it may go so far as to show more extensive disease even with cavitation where none was originally suspected. The type of shadow and its consistency may likewise suggest other possible pulmonary diseases. I cannot emphasize too strongly here that cancer of the lung to be treated successfully surgically must be recognized in an early stage. Hodges found that out of 167 proven pulmonary lesions discovered by photofluorography in a three-months' period, 10 per cent were due to neoplasms.

After a satisfactory film of the chest has been made a careful history should be taken, questioning the patient concerning (1) fatigue, (2) digestive disturbances, (3) cough and (4) loss of weight. Sometimes one or more of these symptoms may have been present but not sufficiently prominent to attract attention. After a careful physical examination a tuberculin test should be applied (1st and 2nd strength purified protein derivative [PPD] or 0.1 mg. of tuberculin [OT] intracutaneously). A negative reaction is of perhaps more value than a positive reaction. If there is no reaction to tuberculin an acute or chronic nonspecific respiratory infection may be the cause of the shadow. An increasing prevalence of coccidioidomycosis is being discovered, and a skin test, if positive, or serologic tests may be carried out to determine its presence. Other fungous diseases produce shadows resembling tuberculosis. If the patient has sputum it should be examined preferably by concentrating three seventy-two hour specimens. If

there is no sputum, gastric lavage should be performed and the contents concentrated and studied by smear and culture or guinea pig

If all results are negative as to the etiology of the x-ray shadows, observation is most important. Some shadows due to acute respiratory disease may clear within a few days or weeks. Those that persist are the important ones, and should be considered to be due to tuberculosis until proved otherwise. Because the shadows appear firm in the first x-ray it is far from wise at that time to state that the disease is healed. Knowing that from the ranks of this asymptomatic group some will enter in the active phases of this disease, we should consider each patient with particular care.

Let us consider the possible forms of treatment in three subdivisions

1 *The Patient Whose X ray Shadows Appear Firm and Are Minimal in Extent*—In the first place, this patient should be told the facts about his disease, its possibilities of spread or regression. He should be put on a daily schedule which allows him to continue his work, if not too arduous, not more than eight hours a day. His diet should be outlined so that he receives a balance of the essential foods with a total caloric value suited to his needs in maintaining a weight which is about 5 to 10 per cent in excess of his average. He should be in bed at least nine hours a night and take a restful day off—at least one in seven. Intemperance in anything should be avoided. This I visualize as a "normal life."

Every month this patient should be rechecked as to progress and preferably fluoroscoped at each of these visits. If all goes well an x-ray is taken within three months and if favorable his visits may be less frequent—one every two or three months for the balance of that year and at six-month periods thereafter for at least a year or two. He should always be particularly careful if he has an acute respiratory infection, for then a small area of tuberculosis may break down and disseminate bacilli. Monthly specimens of sputum should be examined, and if he has no sputum a gastric lavage every three or four months at least during this first year should be done. Of course, his associates should be x-rayed to determine whether he received the infection from them or has given it to them. All this is facilitated by the public health nurse who is part of a Health Department with a modern tuberculosis program. This will be discussed later. In this group Webster found that 10 per cent had either positive sputum or gastric lavage studies. If so, this patient should be placed in a group which is to be treated more actively.

2 *The Asymptomatic Patient with Minimal or Moderately Advanced Disease and in Whom the Shadows Are Fuzzy and with Indefinite Borders but no Cavity Is Visible*—The same routine of standard (preferably stereoscopic) x-rays, history, skin tests and sputum studies is followed as in the previous group, but in addition the patient should be put to bed. If no other cause is found to explain the persistent disease it is

advisable for him to learn how to live with this more dangerous type of disease. Sanatorium care teaches him these points better than home instruction because he lives the right kind of life twenty-four hours every day. Webster found 54.6 per cent of these patients had a positive sputum or gastric specimen obtained by lavage. If his sputum is persistently positive and the shadows do not extensively clear after two to three months, pneumothorax therapy should be strongly considered. Early collapse therapy where rest has not succeeded often closes unseen cavities and the shortened period of sanatorium care may come within the patient's financial abilities. With such a program many patients can afford three to four months in a sanatorium, as against the many months or years required if the disease becomes more extensive. If the pneumothorax is satisfactory—not limited because of adhesions—and is allowed to produce selective collapse, the patient may continue his treatment at home, remaining of course under strict supervision.

**3 Patients Whose X-rays Show More Extensive Disease and the Presence of Cavitation**—The same immediate study should be carried out and if it is positive for tuberculosis the patient should enter a sanatorium at once. If, with rest for a month or six weeks, the lesion has not markedly regressed pneumothorax therapy should be instituted, and the regimen outlined previously carried out. The patient should remain until his sputum is consistently negative—or as Willis has quite expressively called it, "positively negative." He may need forms of collapse therapy other than pneumothorax but these should be carried out while he is under close observation in the sanatorium.

**The Follow-up**—In order that persons who through this survey method are suspected of having tuberculosis may receive prompt care and study, the Public Health Service has formulated the following plan to be carried out everywhere in the county. Selective Service rejectees are all reported to the State and through it to the local Board of Health for further study. In some localities all the men are sent to local clinics and in others those who can afford private care are referred to their physicians for study. Through the help of the local Board of Health and its nursing staff each case can be followed officially, the Health Department receiving reports from clinics or private physicians as to the final diagnosis as well as the presence or absence of tuberculosis in all contacts. In New York City Edwards and his co-workers have been able to study 94 per cent of the rejected men and have found that 8 per cent presented no tuberculosis or that it was clinically compatible with military requirements, and they were sent into the service. Many more in their studies and in the hands of private physicians are at work in industry under proper supervision.

The same general procedure is carried out in large industrial surveys. The State and Local Boards of Health as well as the individuals are notified as to the possibility of tuberculosis and they are sent through the same public or private channels. We, as physicians, should

take this task of diagnosis and treatment seriously for if we do not the Government may take over what now is still in private care. Those who can afford private care of a high standard may avail themselves of it. Those who cannot afford it will be taken care of through the public channels

The strength of any program to find and eradicate tuberculosis is as strong as its weakest link—the proper follow-up. An efficient Health Department with good vital statistics, a sufficient corps of visiting nurses to aid in the follow-up and care of patients, and hospital and sanatorium beds in the ratio of 3 to 4 per death (or in some ratio to the morbidity) from this disease are essential. Many groups must co-operate efficiently to bring about the day when tuberculosis will be a rarity.

Nonofficial (voluntary) agencies, such as the Tuberculosis Associations supported by Christmas Seals, must have an aggressive outlook in this program, often blazing the trail by experiments that cannot be undertaken by the official agencies. They must work most harmoniously with the local and state Boards of Health.

The medical profession must understand the important part it plays in the proper study of each case and in seeing that modern treatment is instituted.

With all this the most recent method of finding tuberculosis—mass x-ray surveys—will go a long way toward eradicating tuberculosis. It is no use struggling to increase the efficiency of x-ray case-finding from 70 per cent efficiency to say, 90 per cent efficiency if (a) the survey cannot be made to cover more than half the population, or (b) if half the cases discovered are permitted to escape from effective supervision.

#### SUMMARY

An effort has been made to describe mass surveys using miniature x-ray films, paper films and the fluoroscope as means for screening out cases of suspected tuberculosis, nonspecific disease of the lungs, early cancer and heart disease. The method may be applied to approximately ten million inductees into the armed forces, or to every patient who comes into a doctor's office.

A single x-ray film, whether it is the standard 14 x 17 inches or a miniature, is not sufficient to make a diagnosis. It must be supplemented by history, laboratory studies and comparative films. If there is any question about the interpretation of an x-ray film it should be studied by an expert. Specialists should also be employed to read the miniature films and the fluoroscopic study.

Because surveys concern persons with a symptomatic tuberculosis the requirements in tact and diligence to keep them properly cared for are much greater than among persons who have symptoms. Note that most of our social mechanism for control of the tuberculosis problem

has been developed on the experience of patients knowingly tuberculous

In the treatment of the asymptomatic case of tuberculosis the patient must be educated on the possibilities of the disease in himself and on the danger of his conveying it to others. Each case must be individualized—some patients may continue at their work if their disease is well controlled and they have periodic rechecks for an indefinite time. They must live a normal life. Others need sanatorium care for education and intensive treatment but this may be relatively short in duration and expense if the disease is amenable to treatment. Collapse therapy after six weeks' or two months' observation often hastens the healing of the disease.

A well planned and efficient program by official and voluntary agencies, the profession and an educated public is necessary for a successful effort in eradicating tuberculosis.

## CUMULATIVE INDEX

- ABORTION early progesterone in, *Jan* 264  
 Achlorhydria acid therapy *March* 426  
 Actinomycosis, *March*, 338  
 Addison's disease desoxycorticosterone acetate in *March* 435  
 Adenoma, parathyroid, *March* 390-393  
 Agglutination test for brucellosis, *March* 353  
 Albumin, human *March* 433  
 Albuminocytologic dissociation in acute infectious radiculoneuritis, *Jan.*, 1  
 Alcohol injections for facial pain *Jan* 77  
 Alcoholism criminal responsibility and, *Jan.*, 212  
 Alloxan in production of diabetes, *March* 436  
 Aluminum hydroxide in hypoparathyroidism, *March*, 435  
     powder in silicosis *March*, 437  
 Amenorrhea hormone therapy, *Jan.*, 258 260 263  
 Amligen *March* 433  
 Amino acids, parenteral use *March* 433  
 Androgen therapy advances in *March* 436  
     in menstrual disorders, *Jan* 265  
 Anemia pernicious *Jan* 229  
     clinical types, *Jan.*, 230  
     liver therapy *Jan.*, 242  
     posterolateral sclerosis in management *Jan* 245  
     suspension of discarded erythrocytes in *March* 432  
 Anemias, macrocytic *Jan.*, 246  
 Anesthesia general, curare in *March*, 423  
     local, new agents, *March* 419  
 Angina pectoris differential diagnosis *March* 513  
     testosterone in *March* 425  
 Ankle clonus in pyramidal tract lesions, *Jan.*, 56  
 Arrhythmias, digitalis in *March*, 531  
     quinidine in *Jan.*, 216  
 Arthritis, rheumatoid neostigmine in *March* 423  
 Aspiration biopsy of liver *March*, 365  
 Aspirin blood coagulation and, *March* 430  
 Asthma bronchial complications, unusual *March* 456  
     military service and *March* 455  
     recent advances *March* 453  
     treatment, *March* 458 461  
 Auricular fibrillation, digitalis in, *March* 532  
     quinidine in *Jan.*, 217  
     flutter digitalis in *March* 532  
     quinidine in *Jan.*, 223  
 Axillary nerve injuries, *Jan.*, 23  
 BABINSKI sign in pyramidal tract lesions *Jan* 47  
 Barbiturates in war psychoses, *March*, 418  
 Behavior Clinic of criminal court *Jan.*, 202  
 Benzadrine in prevention of motion sickness *March* 418  
 Biopsy, endometrial *Jan.*, 252  
     liver by aspiration *March* 365  
 Bladder atony furmethide in *March* 421  
 Blastomycosis, *March* 334  
 Blood coagulation drugs influencing *March*, 430  
 Bones, lesions in hyperparathyroidism *March*, 394 396  
 Brachial plexus injuries, *Jan* 19  
 Bromsalizol *March* 419  
 Bronchial asthma recent advances, *March* 453  
 Brucellin, *March* 359  
 Brucellosis, *March* 343  
 Burns, shock in sodium lactate in *March*, 438  
 CANDIDA albicans, infections with *March* 323  
 Carbon dioxide in bronchial asthma *March* 459  
 Carcinoma of prostate estrogen therapy, *March* 435  
     of stomach diagnosis, *March*, 489  
     gastroscopy in, *March*, 499  
 Catsplexy, potassium chloride in *March* 422  
 Causalgia, *Jan.*, 13  
 Cavernostomy in tuberculosis, *March* 450  
 Cedilanid *March* 424 529  
 Chaddock's sign in pyramidal tract lesions *Jan* 50  
 Chemotherapy in brucellosis, *March* 357  
     in tuberculosis, *March* 445  
 Cholesterothorax, 507 510  
 Choline in cirrhosis of liver *March* 429 484

- Chordotomy for intractable pain, *Jan*, 98
- Choriomeningitis, lymphocytic, benign, *Jan*, 36
- Chromoblastomycosis, *March*, 336
- Chylothorax, 506, 510
- Circus movement, *Jan*, 216
- Cirrhosis of liver, correlation of composite liver function study with liver biopsy, *March*, 363
- diagnosis, *March*, 480
- dietary treatment, *March*, 276, 429, 484, 485
- etiology, *March*, 273, 479
- hypotrophic substances in, *March*, 428, 484
- symptoms and signs, *March*, 275
- treatment, recent advances, *March*, 273, 479
- Clawed hand in ulnar nerve injury, *Jan*, 15
- Clonus in pyramidal tract lesions, *Jan*, 56
- Coccidioidin, *March*, 334
- Coccidioidomycosis, *March*, 332
- Cold, common, propadrine hydrochloride in, *March*, 420
- Colitis, chronic ulcerative, sulfathalidine in, *March*, 427
- Coronary occlusion, quinidine in, *Jan*, 227
- restriction of activity in, and extent of myocardial infarction, *March*, 405
- thrombosis, pain of, differential diagnosis, *March*, 513
- Criminal responsibility, epilepsy and, *Jan*, 212
- insanity and, *Jan*, 195
- mental retardation and, *Jan*, 208
- Cryptococcosis, *March*, 335
- Curare, new uses, *March*, 423
- test for myasthenia gravis, *Jan*, 129
- Cystine in liver disease, *March*, 429
- D-DESOXYEPHEDRINE hydrochloride, *March*, 420
- Dementia praecox, *Jan*, 148
- Demerol, *March*, 417
- Dermatophytosis, *March*, 323
- treatment, *March*, 326
- Desoxycorticosterone acetate in Addison's disease, *March*, 435
- Diabetes mellitus, globin insulin in, *March*, 436
- Diasone in tuberculosis, *March*, 447, 448
- Dichlorophenarsine hydrochloride in syphilis, *March*, 438
- Dicoumarol in prevention of embolism and thrombosis, *March*, 430, 431
- Dienoestrol, *March*, 435
- Diet in cirrhosis of liver, *March*, 276, 427, 484
- in pernicious anemia, *Jan*, 244
- Digilanid, *March*, 423
- Digitaline native, *March*, 423
- Digitalis, blood-clotting and, *March*, 431
- in arrhythmias, *March*, 531
- in heart failure, *March*, 524
- preparations and uses, *March*, 423, 524
- Digitoxin, *March*, 423
- Digoxin, *March*, 424, 529
- Dihydrotachysterol in hyperparathyroidism, *March*, 402
- Dilantin sodium in bronchial asthma, *March*, 459
- Diuretics, new, *March*, 424
- Drop wrist in radial nerve injury, *Jan*, 10
- Dysentery, bacillary, sulfasuxidine in, *March*, 426
- sulfathalidine in, *March*, 426
- Dysmenorrhea, hormone therapy, *Jan*, 259, 262, 265, 267
- ELECTROCARDIOGRAPHY, ventricular gradient in, *March*, 464
- Electrodiagnosis in peripheral nerve injuries, *Jan*, 23
- Electroshock therapy in psychoses with insomnia, *Jan*, 192
- outpatient, in psychiatric disorders, *Jan*, 165
- Embolism, prevention, dicoumarol in, *March*, 430, 431
- heparin in, *March*, 431
- Empyema, pyogenic, 507, 510
- Encephalo-myeo-radiculoneuritis, acute, *Jan*, 1
- Endocarditis, brucella, *March*, 348
- subacute bacterial, therapeutics, *March*, 425
- Endocrine system, therapeutics, *March*, 433
- therapy in menstrual disorders, *Jan*, 251
- Endometrial biopsy, *Jan*, 252
- Enuresis, ephedrine in, *March*, 420
- Ephedrine in enuresis, *March*, 420
- in myasthenia gravis, *Jan*, 134, *March*, 421
- Epidermatophytosis, *March*, 323
- Epilepsy, criminal responsibility and, *Jan*, 212
- glutamic acid in, *March*, 418
- Erb's paralysis in brachial plexus injuries, *Jan*, 19
- Erythrocytes, discarded, suspension of, clinical uses, *March*, 432
- Estrogen therapy in menstrual disorders, *Jan*, 259
- in prostatic cancer, *March*, 435
- new products, *March*, 435

- Ether in oil intramuscularly in bronchial asthma, *March*, 459  
 Ethinyl estradiol *March*, 435  
 Expectorants in bronchial asthma, *March* 458  
 Extrasystoles quinidine in *Jan* 227  
 Eye signs in brucellosis, *March* 347
- FACIAL pain neoplasia as cause *Jan.*, 91  
 relief of *Jan.*, 73  
 symptomatic, *Jan.* 87  
 Fasciculation neostigmine in *March*, 422  
 Feeble-mindedness criminal responsibility and *Jan* 208  
 Feet dermatophytosis of *March* 323  
 Femoral nerve injuries, *Jan.*, 23  
 Ferrous carbonate in facial pain *Jan.*, 77  
 Fever therapy in brucellosis, *March* 360  
 Fibrin foam and film in neurosurgery *March* 432  
 Fluorescence test for dermatophytosis, *March* 325  
 Fractures in hyperparathyroidism, *March*, 394  
 Fungus infections, pleural effusions of *March* 508 511  
 sodium propionate in *March* 438  
 Furmethide in bladder atony *March* 421
- GASTRIC analysis, diagnostic value, *March* 492  
 Gastritis, diagnosis, *March*, 489  
 gastroscopy in *March*, 498  
 Gastroduodenal disease, diagnosis, *March* 489  
 Gastrointestinal tract, therapeutics, *March*, 426  
 Gastroscopy *March* 497  
 Gelatin as substitute for plasma, *March* 433  
 Globin insulin in diabetes, *March* 436  
 Glomerulosclerosis, intercapillary *March* 338  
 Glucosides, cardiac, *March* 423 529  
 Glutamic acid in epilepsy, *March* 418  
 Glycine in myasthenia gravis, *Jan* 135  
 Gonadotropin therapy in menstrual disorders, *Jan* 256  
 Gonda sign in pyramidal tract lesions, *Jan.*, 57  
 Gordon's sign in pyramidal tract lesions, *Jan.*, 53  
 Grafts nerve *Jan.*, 27  
 Groin dermatophytosis of *March* 323  
 Guanidine in myasthenia gravis, *Jan.* 134  
 Guillain Barré syndrome *Jan.*, 1
- HEART disease pain of differential diagnosis, *March* 313  
 quinidine in *Jan.* 215  
 failure, congestive, with hypertension, *March* 547
- Heart failure, digitalis in, *March*, 524  
 lesions in hyperparathyroidism *March*, 395  
 therapeutics, *March*, 423  
 Hematoma subdural *Jan.*, 62  
 Hemorrhage in liver damage, control of *March* 432  
 Hemothorax, *March*, 506, 510  
 Heparin in thrombosis and embolism *March* 431  
 Herniation of intervertebral disk, *Jan* 111  
 Hexestrol *March* 435  
 Histamine azoprotein in bronchial asthma, *March*, 460  
 in migraine, *March*, 438  
 Histoplasmosis, *March* 337  
 Hoffman sign in pyramidal tract lesions, *Jan.*, 54  
 Hormone assays, *Jan*, 254  
 Hydrochloric acid in pernicious anemia *Jan.*, 243  
 Hydrothorax, *March* 506, 510  
 Hyosine in prevention of motion sickness *March* 418  
 Hyperparathyroidism, *March* 389  
 Hyperpyrexia See *Fever therapy*  
 Hypertension arterial kidneys and clinical relationships *March* 535  
 drug therapy *March* 425  
 Hypertrophy, thioracil in, *March* 302 433  
 Hypnotics in insomnia, *Jan.*, 187  
 Hypomenorrhea hormone therapy *Jan.*, 260  
 Hypoparathyroidism treatment *March*, 434 435  
 Hypotension neosynephrin hydrochloride in *March*, 420
- IMMUNE serum in brucellosis, *March*, 359  
 Injuries, peripheral nerve, *Jan*, 9  
 Insanity and the criminal, *Jan.*, 195  
 legal conceptions, *Jan.*, 204  
 malingering and, *Jan.*, 205  
 Insomnia, *Jan.*, 178  
 causes of *Jan*, 180  
 clinical effects, *Jan.*, 181  
 general management *Jan.*, 184  
 hypnotics in, *Jan.*, 187  
 psychotherapy *Jan.*, 186  
 shock therapy in psychotic cases, *Jan.*, 192  
 Insulin globin, in diabetes, *March*, 436  
 shock therapy in psychoses with insomnia, *Jan.*, 192  
 Intervertebral disk protrusion of *Jan* 111  
 Intocostine, *March*, 423  
 Iodides in sporotrichosis, *March* 330  
 Iodine in hyperthyroidism thioracil and *March* 310



- JOLLY's myasthenic reaction, *Jan*, 129
- KEPHRINE hydrochloride, *March*, 420
- Kidneys, arterial hypertension and, clinical relationship, *March*, 535
- lesions, in hyperparathyroidism, *March*, 394
- Klumpke's paralysis in brachial plexus injuries, *Jan*, 19
- LANATOSIDE C, *March*, 424
- Lead poisoning, sodium citrate in, *March*, 437
- Lipotropic substances in cirrhosis of liver, *March*, 428, 483
- Liver, biopsy, by aspiration, *March*, 365
- cirrhosis See *Cirrhosis of liver*
- damage to, hemorrhage in, control of, *March*, 432
- diseases, diet as factor, *March*, 276, 427, 484
- functional tests, composite, *March*, 363
- therapy in pernicious anemia, *Jan*, 242
- Lobectomy in tuberculosis, *March*, 451
- Lung, resection, in tuberculosis, *March*, 451
- Lymphocytic choriomeningitis, benign, *Jan*, 36
- MAGNESIUM sulfate in paroxysmal tachycardia, *March*, 426
- Malingerer of insanity to escape criminal responsibility, *Jan*, 205
- Malta fever See *Brucellosis*
- Mecholyl in bronchial asthma, *March*, 459
- Median nerve injuries, *Jan*, 11
- Median-ulnar nerve injuries, *Jan*, 18
- Medullary tractotomy for facial pain, *Jan*, 84
- Meigs' syndrome, pleural effusion in, *March*, 509, 512
- Meningitis, lymphocytic, benign, *Jan*, 36
- Menorrhagia, hormone therapy, *Jan*, 259, 261, 264, 266
- Menstruation, disorders of, diagnostic aids, *Jan*, 252
- endocrine therapy, *Jan*, 251
- Mental disease, criminal responsibility and, *Jan*, 195
- retardation, criminal responsibility and, *Jan*, 208
- Mercupurin as diuretic, *March*, 424
- Methionine in cirrhosis of liver, *March*, 429, 484
- Microsporon infections, *March*, 323
- Migraine, histamine-azoprotein in, *March*, 438
- Miscarriage See *Abortion*
- Monilia albicans, infections with, *March*, 323, 328
- Monoacetylmorphine, *March*, 418
- Monocaine for local anesthesia, *March*, 419
- Motion sickness, treatment, *March*, 418
- Mouth wash in pernicious anemia, *Jan*, 245
- Musculocutaneous nerve injuries, *Jan*, 23
- Myasthenia gravis, diagnostic tests, *Jan*, 128, *March*, 422
- management, *Jan*, 126, 129
- treatment, advances in, *March*, 421
- Myasthenic reaction of Jolly, *Jan*, 129
- Mycology, medical, *March*, 323
- Myocardial infarction, restriction of activity in coronary occlusion in relation to, *March*, 405
- NEEDLE liver biopsy, *March*, 365
- Neostigmine in fasciculation, *March*, 422
- in myasthenia gravis, diagnostic, *March*, 422
- therapeutic, *March*, 421
- in poliomyelitis, *March*, 423
- in rheumatoid arthritis, *March*, 423
- Neosynephrin hydrochloride, uses, *March*, 420
- Nephrocalcinosis in hyperparathyroidism, *March*, 394
- Nephrosis, testosterone in, *March*, 436
- Nerve grafts, *Jan*, 27
- Nerves, peripheral, injuries, diagnosis and surgical treatment, *Jan*, 9
- Nervous disease, organic origin in apparent functional cases, *Jan*, 30
- system, autonomic, therapeutics, *March*, 419
- central, therapeutics, *March*, 417
- Neuralgia, trigeminal, *Jan*, 73
- atypical, *Jan*, 85
- symptomatic, *Jan*, 75
- Neuromuscular apparatus, therapeutics, *March*, 421
- Neuropsychiatric diseases, symposium on, *Jan*, 1
- Neurosurgery, fibrin film and foam in, *March*, 433
- Neurotomy, retrogasserian, classical, for facial pain, *Jan*, 80
- posterior, for facial pain, *Jan*, 83
- New developments in medicine, symposium on, *March*, 273
- Nocardia asteroides, infection with, *March*, 340
- OCTOFOLLIN, *March*, 435
- Omentopexy in cirrhosis of liver, *March*, 281
- Oniophrenia, *Jan*, 162
- Oppenheim's sign in pyramidal tract lesions, *Jan*, 52
- Opsonocytophagic test for brucellosis, *March*, 354

- Organic origin of apparent functional nervous disease *Jan.*, 30  
 Osteitis fibrosa cystica generalisata *March* 389 395  
 Ouabain *March* 424
- PAIN facial neoplasia as cause *Jan.*, 91  
 relief of *Jan.*, 73  
 symptomatic, *Jan* 87  
 intractable, chordotomy for *Jan* 98  
 precordial differential diagnosis, *March* 513
- Pancreatic insufficiency, pancreatic enzyme in, *March* 429
- Paracetamol in cirrhosis of liver *March* 281
- Paralysis Erb's *Jan* 19  
 familial periodic, thyroid in *March* 422  
 Klumpke's, *Jan.*, 19
- Parasympathomimetic drugs *March* 421
- Parathyroids, diseases of *March* 389
- Paredrine uses, *March* 420
- Paredrinol uses, *March* 420
- Patek's diet in cirrhosis of liver *March* 276
- Petallar clonus in pyramidal tract lesions *Jan.*, 57
- Peptic ulcer benign and malignant, differentiation *March* 495  
 diagnosis, *March* 489  
 gastroscopy in *March* 499  
 roentgen diagnosis, *March* 493  
 sodium alkyl sulfate in *March* 426
- Periarthritis nodosa, *Jan.*, 139
- Peripheral nerve injuries diagnosis and surgical treatment *Jan.*, 9
- Peritoneoscopy in liver disorders, *March* 369
- Pernicious anemia, *Jan.*, 229  
 clinical types, *Jan* 230  
 liver therapy *Jan.*, 242  
 posterolateral sclerosis in management *Jan.*, 245
- Peroneal nerve injuries, *Jan.*, 20
- Pharmacology recent advances, *March* 417
- Phthalylsulfathiazole. See *Sulfathiazole*
- Plasma, bovine, for human use *March* 433
- Pleura, malignant tumors, effusions due to *March* 509 512
- Pleural effusions, diagnosis and treatment *March* 502
- Pneumectomy in tuberculosis, *March* 451
- Pneumonia, pneumococcal sulfamerazine in, *March* 294
- Poliomyelitis, neostigmine in *March* 423
- Polyuria in hyperparathyroidism, *March* 395
- Potassium chloride in cataplexy, *March* 422  
 in myasthenia gravis *Jan* 135
- Pourougin *March*, 423
- Precordial pain differential diagnosis *March* 513
- Pre-eclampsia *March*, 538 541
- Pregnancy macrocytic anemia of *Jan* 247
- Procaine hydrochloride for local anesthesia *March* 419
- Progesterone therapy in menstrual disorders *Jan* 263
- Promin in tuberculosis *March* 447 448
- Propadrine hydrochloride in coryza *March* 420
- Propionate propionic acid ointment in dermatophytosis, *March* 326
- Prostate carcinoma, estrogen therapy *March* 435
- Prostigmine in myasthenia gravis, *Jan.*, 131  
 diagnostic test, *Jan.*, 128
- Protrusion of intervertebral disk, *Jan.*, 111
- Psychiatrist function of in court, *Jan.*, 211
- Psychoses, criminal responsibility in *Jan* 195  
 electroshock therapy outpatient, *Jan.*, 165  
 war barbiturates in, *March* 418  
 with insomnia electroshock and in insulin shock therapy *Jan* 192
- Psychotherapy in insomnia, *Jan* 186
- Pyelonephritis, atrophic *March* 541  
 in hyperparathyroidism *March* 394
- Pyramidal tract signs, pathologic, *Jan.*, 45
- QUINIDINE in auricular fibrillation *Jan.*, 217  
 in auricular flutter *Jan.*, 223  
 in paroxysmal tachycardia *Jan* 226  
 uses and abuses, *Jan* 215
- Quinine test for myasthenia gravis *Jan.*, 179 *March* 422
- RACEPHEDRINE hydrochloride *March* 420
- Radial nerve injuries, *Jan.*, 10
- Radiculoneuritis acute infectious, *Jan* 1
- Retrogasserian neurotomy classical for facial pain *Jan.*, 80  
 posterior for facial pain *Jan.*, 83
- Rheumatic fever pleural effusion in, *March* 503
- sodium salicylate in *March* 425
- sulfadiazine in, prophylactic, *March* 425
- Rheumatoid arthritis, neostigmine in, *March* 423

- Ringworm, *March*, 323  
 Roentgen diagnosis of carcinoma of stomach, *March*, 495  
   of peptic ulcer, *March*, 493  
   of tuberculosis, rapid screening methods, *March*, 54  
 Rossolimo sign in pyramidal tract lesions, *Jan*, 53
- SALYRGAN-THEOPHYLLINE as diuretic, *March*, 424  
 Sandoz, 424  
 Scalp, dermatophytosis of, *March*, 323  
 Schizophrenia, *Jan*, 150  
   modern concept of, *Jan*, 147  
 Sciatic nerve injuries, *Jan*, 20  
 Sclerosis, posterolateral, management in pernicious anemia, *Jan*, 245  
 Shock in burns, sodium lactate in, *March*, 438  
   therapy of psychoses, *Jan*, 165  
   prevention of fractures, curare for, *March*, 423  
 Silicosis, aluminum powder in, *March*, 437  
 Skin tests in brucellosis, *March*, 354  
 Sleeplessness, *Jan*, 178  
   clinical effects, *Jan*, 181  
   treatment, *Jan*, 184  
 Sodium alkyl sulfate in peptic ulcer, *March*, 426  
   citrate in lead poisoning, *March*, 437  
   lactate in burn shock, *March*, 438  
   propionate in fungus infections, *March*, 438  
   salicylate in rheumatic fever, *March*, 425  
 Spiller-Frazier operation for facial pain, *Jan*, 80  
 Spontylitis, brucella *March*, 351  
 Sporotrichosis, *March*, 328  
 Steam inhalations in bronchial asthma, *March*, 458  
 Steatorrhea, pancreatic, pancreatic enzyme in, *March*, 429  
 Sterility, hormone therapy, *Jan*, 258, 261  
 Stomach, carcinoma, diagnosis, *March*, 489  
 Streptotrichosis, *March*, 340  
 Strophanthin in heart failure, *March*, 529  
 Subdural hematoma, *Jan*, 62  
 Succinylsulfathiazole See *Sulfasuxidine*  
 Sulfadiazine in rheumatic fever, prophylactic, *March*, 425  
 Sulfamerazine in pneumococcal pneumonia, *March*, 294  
 Sulfasuxidine in bacillary dysentery, *March*, 426  
 Sulfathalidine in bacillary dysentery, *March*, 426  
   in chronic ulcerative colitis, *March*, 427
- Sulfonamides in brucellosis, *March*, 357  
   in tuberculosis, *March*, 447  
   insoluble, in intestinal diseases, *March*, 426  
 Suprapatellar reflex in pyramidal tract lesions, *Jan*, 57  
 Suture, primary, in peripheral nerve injuries, *Jan*, 25  
 Sympathomimetic drugs, new, *March*, 419  
 Syphilis, dichlorophenarsine hydrochloride in, *March*, 438
- TACHYCARDIA, paroxysmal, digitalis in, *March*, 531  
   magnesium sulfate in, *March*, 426  
   quinidine in, *Jan*, 226  
 Talma operation in cirrhosis of liver, *March*, 281  
 Testosterone in menstrual disorders, *Jan*, 265  
   in nephrosis, *March*, 436  
 Tetanus, curare in, *March*, 423  
 Tetany, parathyroid, prevention, *March*, 402, 434  
 Thiamine hydrochloride in facial pain, *Jan*, 77  
 Thiouracil, clinical development and application, *March*, 303, 306  
   in thyrotoxicosis, *March*, 302, 433  
   toxicity, *March*, 307  
 Thoracentesis, *March*, 503  
 Thoracoplasty in tuberculosis, *March*, 449  
 Thrombosis, coronary, *March*, 405  
   pain of, differential diagnosis, *March*, 513  
   venous, heparin in, *March*, 431  
 Thrush, *March*, 323, 328  
 Thymectomy for myasthenia gravis, *Jan*, 136  
 Thyroid in familial periodic paralysis, *March*, 422  
 Thyrotoxicosis, thiouracil in, *March*, 302, 433  
 Tibial nerve injuries, *Jan*, 22  
 Tinea, *March*, 323  
 Torulosis, *March*, 335  
 Tractotomy, medullary, for facial pain, *Jan*, 84  
 Transfusions, blood, in pernicious anemia, *Jan*, 245  
 Trichlorethylene in facial pain, *Jan*, 77  
 Trichophytin test for dermatophytosis, *March*, 325  
 Trichophytosis, *March*, 323  
 Trigeminal neuralgia, *Jan*, 73  
   atypical, *Jan*, 85  
   symptomatic, *Jan*, 75  
 Trigger zones in trigeminal neuralgia, *Jan*, 74  
 Trömner's technic for Hoffmann sign, *Jan*, 54

- Tuamine sulfate, *March* 420  
 Tuberculosis, pulmonary asymptomatic  
   case management *March* 550  
   chemotherapy, *March* 445  
   dlasone in *March* 447 448  
   modern methods of finding *March*  
     544  
   pleural effusions of, *March* 507, 511  
   promin in *March* 447 448  
   surgical treatment *March* 449  
   treatment recent advances *March*,  
     445  
 Tularemia, pleural effusion in *March* 508  
 Tumors, facial pain due to *Jan* 91  
  
 ULNAR nerve injuries, *Jan* 15  
 Ulnar median nerve injuries *Jan.*, 18  
 Undecylenate undecylenic acid ointment  
   in dermatophytosis, *March* 326  
 Undulant fever See *Brucellasis*  
 Uroguin in heart failure, *March* 529  
  
 Uterine bleeding functional, hormone  
   therapy *Jan.*, 259 261 264 266  
  
 VACCINES in brucellosis, *March* 358  
 Ventricular gradient, *March* 464  
 Veritol *March* 420  
 Vesania *Jan.*, 147  
 Vitamin C in bronchial asthma *March*  
   460  
 Vitamin D massive doses, in prevention  
   of parathyroid tetany *March* 434  
 Vitamin K, massive doses, with dicou  
   marol *March* 430  
 Vitamin therapy in cirrhosis of liver  
   *March* 279  
   in pernicious anemia. *Jan.*, 244  
  
 WASSERHELLE cell *March* 400  
 Wrist clonus in pyramidal tract lesions,  
   *Jan.*, 57



*This edition is produced in compliance with the Government's regulations for conserving paper and other essential materials*

## CONTENTS

### SYMPOSIUM ON INTERNAL MEDICINE IN GENERAL PRACTICE

	PAGE
Introduction Modern Trends in Internal Medicine By Dr Russell L. Cecil	563
Environmental Factors in the Etiology of Rheumatic Conditions By Dr Russell L. Cecil	566
Present Day Treatment of Nontuberculous Renal Infections By Dr Meredith F. Campbell	571
Penicillin Versus Sulfonamide Therapy By Lt. Colonel A. Allen Goldbloom and Major Emanuel H. Nickman, M.C., A.U.S.	579
The Use of Electrocardiograms in Medicine By Dr Harold J. Stewart	590
* The Differential Diagnosis of Peptic Ulcer By Dr I. W. Held	624
Diverticulosis and Diverticulitis A Clinical Study of the Complications By Drs Kirby A. Martin and Charles G. Adsit, Jr	639
* Treatment of Cirrhosis of the Liver by Nutritional Means By Drs Norman Jolliffe and Elmer Alpert	655
Lymphogranuloma Venereum By Drs. Robert B. Greenblatt and Paul L. Wermer	663

FROM THE HAMMOND GENERAL HOSPITAL, MODESTO, CALIFORNIA

Penicillin Resistant Gonorrhea By Captain Richard L. Saunders and Captain Murray M. May, M.C., A.U.S.	688
--	-----

# CONTENTS

	PAGE
Acute Acquired Hemolytic Anemia	695
By Lt Colonel Garnett Cheney and Major Edward J Denenholz, M C, A U S	
The Fundamental Importance of Diet in the Treatment of Peptic Ulcer in an Army General Hospital	706
By Major Virgil J Gianelli and Captain Vincent Bellafiore, M C, A U S	
SYMPOSIUM ON REHABILITATION	
Introduction	714
By Colonel Howard A Rusk, M C, A. U S	
Convalescent Care and Rehabilitation in the Army Air Forces	715
By Colonel Howard A Rusk, M C, A U S	
Psychiatric Disorders in Combat Crews Overseas and in Returnees	729
By Lt Colonel Roy R Grinker, M C, A A F	
Psychosomatic Aspects of Rehabilitation	740
By Major Albert A Rosner, M C, A U S	
Reconditioning of Transitorily Maladjusted Soldiers	751
By Colonel Thomas G Tousey, M C, U S Army	
Reconditioning the Malaria Patient	760
By Captain William L Noe, Jr and Major Earl W Parks, M C, A U S	
The Convalescent Care of Rheumatic Fever in the Army Air Forces	765
By Lt Colonel Irving Ershler, M C, A U S	
Fatigue and Exhaustion States in the Army and in Industry	771
By Dr Joseph L Fetterman, Major, M C, U S Army (Ret)	
Physical Medicine in Medical Rehabilitation	786
By Drs Gordon M Martin and Frank H Krusen	
Nutrition in Rehabilitation	794
By Dr Tom D Spies	
The Problem of Rehabilitation in Civilian Medical Practice	807
By Dr William Benham Snow	
Cumulative Index	822

# THE MEDICAL CLINICS of NORTH AMERICA

---

NEW YORK NUMBER

---

## SYMPOSIUM ON INTERNAL MEDICINE IN GENERAL PRACTICE

---

### INTRODUCTION MODERN TRENDS IN INTERNAL MEDICINE

DURING the past twenty years of my experience as a practitioner and teacher, as well as editor of a textbook, certain trends have become apparent in the field of internal medicine. The reading of the excellent contributions in this number of the *Medical Clinics of North America* serves to accentuate this fact. Internal medicine changes as medical science develops, and sometimes these changes take place with remarkable rapidity. As examples, one thinks immediately of chemotherapy in the field of infectious diseases, and the recent remarkable developments in endocrinology. These changes are so obvious as to hardly be worthy of comment. What I have in mind are rather the more gradual changes in point of view, so to speak, which are noticeable as one follows the trend of medical literature from year to year. Let me briefly refer to some of these trends.

1 *The trend away from emphasis on pathological anatomy to emphasis on pathological physiology*, or to put it in another way the change of interest from structure to function. The brilliant contributions of Virchow and his contemporaries in pathology had an enormous influence on the internal medicine of Osler's time. As a result, Osler's textbook and to a less extent other medical monographs which were published at the turn of the century, gave a great deal of space to the discussion of pathological anatomy. The trend toward physiology was brought about by the rapid advances in physiology and biochemistry. This additional knowledge concerning human physiology, both normal and pathological, greatly widened the internist's concept of disease and put modern therapeutics on a rational basis.

2 *The trend away from emphasis on infectious diseases to chronic constitutional disease*. This trend of course is obvious to every internist and the reason for it is also clear. Infectious diseases have in great measure been brought under control. Chronic systemic disease is still



pretty much an unsolved problem. No doubt the increasing average age of our population is another contributing factor, and in part explains the recent appearance of a number of articles and monographs on geriatrics. The problem of chronic disease becomes increasingly fascinating to the internist, and certainly he approaches it with much more optimism than did the previous generation of physicians.

3 *The rapid development of subspecialties in the field of internal medicine.* We have had gastroenterologists, cardiologists and neurologists for some time past, but during the last few decades a great variety of new specialties have appeared in the field, and many internists are devoting almost their entire time to such subjects as tuberculosis, diabetes, arthritis, allergic diseases and disorders of the endocrines. Personally I believe this is a wholesome trend. However, it is very important for these highly specialized practitioners to maintain their contacts with the whole field of internal medicine. Otherwise they become so narrow in their point of view that their approach to all medical problems is completely dwarfed, and because of their lack of facility and skill in other lines, they lose the proper perspective in both the diagnosis and treatment of their particular specialty.

The rapid development of these subspecialties makes it difficult at times for the general practitioner to discover just what constitutes his domain today in the field of practice. Perhaps the establishment of group clinics will lead to a solution of these confused borderlines.

4 *The rapidly increasing number of laboratory tests.* Such procedures all have their place in modern medicine, but it would seem as though the great multiplicity of these tests in some particular fields, such as liver function, have grown to a point where some birth control were indicated! Several problems arise in connection with modern laboratory studies. One is the cost to the patient, the other, proper understanding and interpretation of these tests by the physician. It is all very well for the internist to be told that the plasma calcium is high and the plasma phosphorus low in osteitis fibrosa cystica, but it is much more important for the physician to know just why these abnormalities have occurred and what significance they have in the handling and treatment of the patient.

5 *The restoration of neurology as an integral part of internal medicine.* For a while it looked as though this important branch would be completely severed from the parental tree! However, the modern tendency is more and more toward an approachment between internal medicine and diseases of the nervous system. In many of our large medical clinics, nervous diseases are now included as a part of internal medicine, and the professor of nervous diseases has the title of professor of medicine. Neurology cannot function without internal medicine. Internal medicine is incomplete without neurology.

6 *The growing emphasis on psychiatry in solving the problems of internal medicine.* This emphasis is observed in the approach not only

to functional disease, but to organic disease as well. The medical students of today are infinitely better equipped in the methods of psychiatry than were the physicians of the last generation. This change in point of view should inevitably lead to better handling of the psychoneurotic patient.

7 *Increasing interest in the social aspects of medicine and the widening field of industrial medicine* The modern physician is becoming more and more interested in the family background of the patient and his home environment. Dr. Henry B. Richardson has just published a fascinating book on the relation of the patient to his family.\* More and more the physician is studying the environment of his patient, both at home and in industry, and is finding it a fruitful field for better understanding of the causes of disease. It is because of the writer's own interest in the patient's environment that he is contributing a short article to this symposium on environmental factors in the etiology of rheumatic pain. More careful investigation of home and industry in relation to disease will continue to throw important light on the pathogenesis and treatment of many medical ailments.

RUSSELL L. CECIL, M.D.

\* Richardson, Henry B. *Patients Have Families*. New York: The Commonwealth Fund, 1945.

## ENVIRONMENTAL FACTORS IN THE ETIOLOGY OF RHEUMATIC CONDITIONS

RUSSELL L. CECIL, M D , S c D , F A C P \*

It is customary for teachers of medicine to stress the importance of history-taking in the examination of a new patient, and certainly nothing is more important in arriving at an accurate solution of the patient's problems. However, many of us in medical school learn things which we promptly forget to apply in practice. In my own experience, I have been frequently amazed at how little effort has been made on the part of the family physician to explore into the daily habits and environment of the patient in order to locate the cause of his trouble. This is well illustrated in the field of rheumatic conditions. I would like to discuss briefly the importance of environmental factors in relation to arthritis, gout, fibrositis and certain other unclassifiable arthralgias.

**Rheumatoid Arthritis.**—In the case of rheumatoid arthritis we are dealing with a disease of unknown etiology. Infection is supposed to play an important part, but in my opinion psychic factors are of even greater importance in initiating the original symptoms or in bringing about a relapse. The psychic traumas most frequently responsible are marital unhappiness, the death of a near relative, financial disaster, long-cherished resentment over some real or fancied injury, and loneliness, which may be extreme, even in the most populous communities. One of the commonest predisposing causes of arthritis in women is the long-sustained anxiety, plus the physical exertion, which results from nursing an aged father or mother over a period of months or even years. I have seen several cases of rheumatoid arthritis develop in young wives whose husbands are overseas with the armed forces. One recent rheumatoid patient developed her first symptoms of arthritis the day following the classification of her husband as 1-A<sup>1</sup>.

The role of climate in the etiology of rheumatoid arthritis is a very definite one, but a factor which is not well understood. Rheumatoid arthritis is primarily a disease of the temperate zone, but it is not unusual to encounter the disease in subtropical climates. Exposure to dampness and cold has some importance also. A good many young men are developing rheumatoid arthritis in our army. However, just how much of this is due to exposure and how much to psychic trauma it is hard to say.

---

\* Professor of Clinical Medicine, Cornell University Medical College, Attending Physician, New York Hospital, Visiting Physician, Bellevue Hospital, New York City

**Osteoarthritis**—If psychic trauma is a major factor in the development of rheumatoid arthritis, *physical* trauma is the important predisposing agent in the etiology of osteoarthritis. Indeed, unless the role of physical trauma is appreciated by the physician in his approach to this disease, his therapy will often end in failure. The physical trauma may occur in the form of one single severe episode, such as intra-articular fracture or dislocation of a joint, or it may be a long series of repeated minor insults. Many an old college athlete in his later years pays highly in physical discomfort for the athletic trophies which he won in school and college. The student of rheumatism encounters these cases frequently in private practice. In the clinic one is more likely to find osteoarthritis as the result of falls, accidents and the like. Much more frequently, however, this very prevalent disease is caused by repeated minor injuries: osteoarthritis of the spine in manual laborers or middle-aged tennis players, osteoarthritis of the hip in truck-drivers and pole-vaulters, osteoarthritis of the shoulder in streetcar conductors, osteoarthritis of the knees in obesity or in old football or baseball stars. In many cases the cause of the osteoarthritis is not at once discernible. Only by careful inquiry and going back into the habits and sports of early life will a basis for the trouble be discovered.

I know of no statistical figures on the relative incidence of osteoarthritis in temperate and in tropical climates. My surmise would be, however, that osteoarthritis, like rheumatoid arthritis, is much commoner in the temperate zone. Certainly the people who have lived hard and exposed lives appear to be more prone to degenerative arthritis than those whose circumstances are more fortunate. The gnarled hands of the farmer come inevitably to mind. I have often noticed how individuals whose work requires constant submergence of the hands in cold water are prone to develop osteoarthritis in later years.

**Gout**—It is possible for an individual to have a gouty diathesis, with high blood uric acid levels and even the renal complications of gout, without any joint manifestations. However, this is *unusual*. The great majority of gouty patients sooner or later have attacks of gouty arthritis. What interests us for the moment are the environmental factors which are instrumental in bringing on the acute attacks of arthritis. The most important provocations of gouty arthritis are trauma and dietary indiscretions. Undoubtedly the prevalence of gouty arthritis in the metatarsophalangeal joint of the great toe is due in large part to the trauma to which this joint is subjected in walking and in other forms of active exercise. The gouty attack may be precipitated by such minor trauma as an unusually long walk or bicycle ride, an excessive amount of golf or tennis, or even too much lawn mowing. According to Hench the inflammatory reaction in posttraumatic gouty arthritis is usually delayed several hours after the trauma, in this respect differentiating the condition from a true traumatic arthritis in

which the discomfort and inflammatory reaction begin immediately after the trauma

Gouty arthritis is often brought on by dietary excesses, such as occur on birthdays, weddings, Thanksgiving and other holidays. On hunting and fishing trips indiscretions of diet may be combined with trauma, an almost perfect combination of predisposing factors. It is important to remember that surgical operations, transfusions and certain drugs, such as salyrgan, ergotamine tartrate, thiamine hydrochloride, insulin and decholin may provoke an attack of gout.

**Fibrositis and Other Unclassifiable Arthralgias**—In this group of cases environmental factors play a much more important role than is generally suspected. First of all, we are dealing in the majority of cases with a psychoneurotic patient. This fact in itself explains certain pains which are possibly imaginary. However, many of these patients, while they are nervous individuals, are having real pain in their joints or muscles. One of the commonest of these conditions is *stiff and painful neck*, often associated with occipital headache, a syndrome which Harold Wolfe has termed "tension headache." This condition may result entirely from an anxiety state. Other factors, however, which have to be considered are posture, eyestrain and osteoarthritis of the cervical spine.

Another extremely prevalent form of "rheumatic" pain is *lumbago*, or so-called "back strain." Many of these are referable to protrusion or rupture of an intervertebral disk, a condition in which trauma plays a very important part. Backache of a less severe character may be due to faulty posture or instability of the lumbar spine, but in many such cases the pain is actually due to occupational strain such as carrying heavy bags or suit cases, excessive and strenuous labor or extreme indulgence in sports such as golf, tennis or baseball. Too often, in my experience, back pain which is referable to occupational or other environmental factors is incorrectly attributed by the physician to osteoarthritis of the lumbar vertebrae, especially in those cases in which the radiologist has reported osteoarthritis in this locality. In view of the fact, however, that practically every normal individual over 45 years of age will show some radiographic evidence of hypertrophic spondylitis, the assumption that lumbar pain is referable to these changes is a dangerous one. In cases in which the bony changes are marked, it is safe to conclude that they have some bearing on the patient's symptoms. Nevertheless, it is surprising how many individuals with marked osteoarthritis of the spine are entirely comfortable, and it is also noteworthy that many patients with lumbar osteoarthritis will be relieved of their backache when they cease from certain activities in work or recreation which have been largely to blame for their discomfort. Bad posture is an important factor in the etiology of back pain and should always be carefully investigated in a patient with this complaint. Even when the posture is apparently good, inquiry into the

individual's habits of life may reveal that he is standing too much, sitting in an uncomfortable chair, sleeping on a sagging mattress or wearing improper shoes

One of the commonest causes of backache in elderly people is gardening. Gardening may also be blamed for pain in the knees when the patient assumes a kneeling position for long periods of time without any protection against the hard cold ground. Strange as it may seem, I have known arthralgia in the knees to result from excessive kneeling in prayer. Excessive stepclimbing is another prevalent method of acquiring pain and stiffness in the knees.

*Pain and stiffness in the shoulder* is usually due to calcific deposits in the subacromial bursa or to so-called peritendinitis of the long tendon of the biceps. Many of these "frozen shoulders" can be traced directly to trauma, either occupational or from overindulgence in sport. *Sciatic pain* is usually the result of pressure at some point in the sacral plexus. Fibrositic pains in the buttocks often simulate sciatic pain and may result from a variety of strains. One of the commonest is driving a car with a stiff clutch or foot-brake. I was recently consulted by a middle-aged woman with sciatic pain. Many questions were propounded in an effort to locate the cause of her disability. All forms of muscle strain were denied. I had given up in despair, went ahead with my physical examination and gave the usual advice concerning rest, physiotherapy, and so forth. As she was taking leave of my office she asked quite innocently if her discomfort could possibly be the result of bowling! Incidentally I know of no sport which can raise more havoc with the back and legs of an elderly individual than bowling, especially if one has not been accustomed to this form of exercise.

#### CONCLUSIONS

What may we conclude from the foregoing remarks? The most important conclusion is that a large number of trivial pains and aches, as well as some of the more serious ones, result from trauma incurred either in one's daily occupation or from indulgence in some sport. Just as important are the psychogenic factors. Finally we must not omit the pains and aches which result from improper posture when sitting or standing.

When a patient consults me for pain in his arm, the first question I ask is "What are you *doing* with your arm?" If the pain is in the leg "What do you *do* with your legs?" These questions, however, are not enough. Many patients will fail to provide a clue, so the physician must make his questions more specific. Many of these pains and aches which result from environmental factors will disappear almost over night when the cause is removed. Unfortunately there is a large group of patients whose pains result from their occupation, yet who are in no position to change their vocation. In such cases about all one can do is to reassure the patient and give him certain simple

suggestions regarding rest and the use of heat and aspirin which may help him over the rough spots

Psychiatric problems can often be solved by the general practitioner, but in the more difficult cases the neuropsychiatrist will be needed. After all, one can endure a certain amount of discomfort philosophically if he understands that the condition is not serious and not likely to increase in severity. I have often remarked that a large part of my working hours was consumed in telling patients that they did *not* have arthritis or neuritis, and that the pain in their arm or leg or back was something that could readily be corrected by proper readjustment to their environment.

# PRESENT DAY TREATMENT OF NONTUBERCULOUS RENAL INFECTIONS

MEREDITH F. CAMPBELL, M.D.\*

WHEN urinary infection is denoted by the demonstration of bacteria in the properly collected specimen, the kidneys and upper urinary tract must be assumed to be involved until adequate examination proves otherwise. It is recognized that often enough the bacterial invasion is limited to the lower urinary apparatus (bladder, urethra, prostate, and so forth) but far more frequently the lower tract manifestations reflect unsuspected and overlooked infection of one or both kidneys. Moreover, the clinical and therapeutic aspects of urinary infection are fundamentally identical whether the patient is four or forty. By custom urinary infections in infants and children have been divorced from infections in adults. Yet the basic considerations are the same with the striking exception that in early infancy the maintenance of nutrition must sometimes take precedence over direct chemotherapeutic attack on the infection itself.

## DIAGNOSTIC STUDIES

The demonstration of pyuria in the properly collected specimen almost always signifies urinary infection. amicrobic pyuria is rare but in recent months several series of cases of this clinical entity have been recorded. Some observers believe the condition is due to virus infection; doubtless it is often unrecognized urinary tuberculosis.

**Collection of the Urine**—Pyuria having been demonstrated as an accidental finding in patients with unsuspected asymptomatic urinary infection, or by routine urinalysis in patients believed to have acute or chronic infection, further laboratory study of the urine is indicated. Here the proper collection of the urine specimen is of paramount importance. When urinary infection is under study in the female, an accurate estimation of pyuria and identification of the bacterial invader demands that the specimen be taken by catheterization whether the patient is newborn or aged. No amount of scrubbing of the female genitalia will permit the passage of a bacteriologically uncontaminated specimen. As a rule, in the male, a satisfactory specimen can be obtained without catheterization: the prepuce is widely retracted, the glans penis and meatus are well washed with oxymercurochrome or bichloride of mercury 1:500 after which the patient voids. When a small amount of urine has been passed, the sterile vessel to collect the specimen is

---

\* Professor of Urology, New York University College of Medicine, New York City.



introduced into the voided urinary stream. Unless this procedure can be carefully carried out, aseptic catheterization is employed.

**Analysis of the Specimen**—The properly collected fresh or well-shaken uncentrifuged specimen is then analyzed routinely with special emphasis on the microscopic examination. Normally the kidneys excrete 300,000 to 500,000 leukocytes in a twelve-hour period and this may cause the appearance of 1 or 2 cells per high power field of uncentrifuged urine. More than 3 to 5 cells per high power field may be considered of clinical importance. No cell should be identified as a pus cell which does not show the lobed polymorphic nucleus, which is readily demonstrable by the addition of a drop of 1 per cent acetic acid to the slide preparation. Too often desquamated epithelial cells are reported as pus cells. The estimation of the pus cell content by examination of centrifuged urine specimens is wholly misleading, but if fresh unsedimented urine is periodically examined during the illness period, satisfactory deductions as to therapeutic success may be made.

**Identification of the Invading Organism**—Bacteriologic investigation is accomplished by urine culture or by Gram stain of the sediment of a centrifuged specimen. The correct identification of the invading bacteria is of paramount importance in the selection of chemotherapy (see tabulation). For example, on a bacteriologic basis, mandelic acid compounds and sulfonamides can be employed almost interchangeably, except that the ammoniogenic *proteus bacillus* is rarely eradicated by mandelic acid compounds yet is readily susceptible to sulfonamide therapy. *Streptococcus faecalis*, the so-called enterococcus, is decidedly sulfonamide-resistant but usually responds favorably to mandelic acid therapy. Penicillin is effective against most gram-positive coccal infections of the urinary tract but is inert against organisms of the *colon-typhoid* group, *proteus bacillus*, and *enterococci* (*Streptococcus faecalis*)—bacteria which commonly invade the urinary tract. In short, rational treatment of urinary infections demands that the etiologic organisms be precisely identified, and when intensive chemotherapy fails to cure the acute disease within two weeks or chronic urinary infection within one month, a thorough urologic investigation is indicated, at which time a more precise anatomic diagnosis usually can be made. Urinary infection persisting more than one month may be considered chronic. In persistent hyperacute renal infections showing no improvement with four to six days of intensive medicinal treatment, complete urologic examination is also indicated.

#### TREATMENT

With the foregoing basic considerations in mind, we proceed to the active treatment of the infection and this will be guided in considerable measure by the severity of the disease and whether acute or chronic. In most instances of acute infection, the patient can take the indicated dose of antiseptic by mouth but in some critically ill, de-

hydrated patients, medication must be administered intravenously, particularly when there is persistent vomiting. As a rule the chosen antiseptic should not be given continuously for more than eight to ten days; failure to observe this dictum accounts for many instances of drug intolerance or severe reaction. It is essential in the treatment of both acute and chronic infection that free bowel elimination be maintained, at least one copious movement per day. This usually means that a laxative must be administered, in acute renal infection repeated colonic irrigations, using large amounts of water (7 to 10 gallons) are particularly beneficial. Demonstrable focal infections should be drained or eradicated; yet, in practice, careful search usually fails to reveal the primary bacterial focus.

Known obstruction along the urinary tract should be counter-attacked as well as possible (catheter, dilation, and so forth) and compatible with the condition of the patient, and eventually eradicated when the clinical condition permits.

It is a urologic axiom that urinary obstruction predisposes to the development of infection and, once infection is established in the presence of obstruction, the infection can rarely be eradicated until the obstruction has been eliminated. Yet with the advent of the more powerful urinary antiseptics such as mandelic acid compounds, the sulfonamides and penicillin, we are now able to sterilize the urine in many patients with urinary obstruction in whom the formerly employed antiseptics were ineffective. In other words, cure of the urinary infection by the administration of methenamine (urotropin) is presumptive evidence that no important urinary tract obstruction exists. On the other hand, no patient cured of persistent infection by the newer urinary antiseptics should be discharged without the benefit of a satisfactory examination of the upper urinary tract by excretory (intravenous) urography. Moreover, an estimation should be made of residual urine as a manifestation of obstructive or neuromuscular vesical uropathy. Most persistent urinary infections are perpetuated by obstruction and/or urinary stasis, and the fact that an infection persisted prior to its eradication by the newer and more effective urinary antiseptics is presumptive evidence that a stasis-producing condition exists. The clinical importance of this observation cannot be overemphasized: if the patient is discharged as cured of urinary infection but with the persistence of an unsuspected obstructive lesion, not only is insidiously progressive and increasingly severe back pressure renal damage permitted to ensue, but the patient is more likely to suffer recurrent infection because of the predisposing factor of urinary obstruction.

**Test of Cure**—No patient should be discharged as cured of his urinary infection until at least two negative bacteriologic examinations of the properly collected specimen (*vide supra*) have been obtained. My preference is urine culture, but several laboratory workers believe that

# CHEMOTHERAPY OF NONTUBERCULOUS URINARY INFECTIONS

<i>Sulfonamides</i>		<i>Mandelic Acid</i> (Calcium or Ammonium Salt)	<i>Penicillin</i>
Dose in 24 Hours, Grams	Under 2 years, 0.5-0.75 2-4 years, 0.75-1.5 5-8 years, 1.0-2.0 9-12 years, 1.5-2.0 Adults, 2.0-4.0	2-4 4-6 5-8 8-12 10-15	5000 to 25,000 units intramuscularly q 3h or 50,000 to 100,000 units intravenously (continuous drip) for 2-4 days according to age and size of patient and severity of infection
BACTERIOLOGIC INDICATIONS	Gram-negative bacilli (B coli, B lactus aerogenes, typhoid) Staphylococcus Streptococcus, hemolytic Proteus Pyocyanus (Pseudomonas)	Gram-negative bacilli (B coli, B lactus aerogenes, typhoid) Staphylococcus Streptococcus hemolytic and non-hemolytic Enterococcus (Streptococcus faecalis) Pyocyanus (Pseudomonas)	Staphylococcus aureus Staphylococcus albus Streptococcus salivarius Streptococcus pyogenes Diplococcus pneumoniae Neisseria gonorrhoeae Neisseria intracellulans Bacillus anthracis Clostridium perfringens (welchii) Clostridium septicum Clostridium tetani Clostridium botulinum Corynebacterium diphtheriae Vibrio comma Actinomyces bovis Streptobacillus moniliformis Borrelia novyi (spirochete of relapsing fever) Treponema pallidum
INEFFECTIVE AGAINST	Enterococcus (Streptococcus faecalis)	Proteus (unless urine highly acid)	Escherichia coli Eberthella typhosa Shigella dysenteriae Salmonella paratyphi Salmonella enteritidis Streptococcus faecalis Klebsiella pneumoniae (Friedlander's bacillus)
URINE REACTION*	Preferably alkaline, coadminister sodium bicarbonate or potassium citrate q.s	Must be more acid than pH 5.5 Mandelic acid concentration greater than 0.5 per cent Ammonium chloride Calcium chloride Ammonium nitrate Dilute hydrochloric acid q.s	Brucella melitensis Pasteurella tularensis Proteus vulgaris Pseudomonas aeruginosa Haemophilus influenzae Monilia albicans Monilia candida Monilia krusei Mycobacterium tuberculosis Blastomyces Trypanosoma lewisi Toxoplasma

\*est estimated by potentiometer or nitrazine solution or paper

examination of the gram-stained centrifuged urine sediment is equally accurate and a few believe the method is even more precise than culture. We employ both methods but chiefly culture, occasionally examination of the gram-stained sediment will reveal organisms when the culture is sterile, but in our experience the reverse has been more often true. Unless the urine is sterilized, the patient is not cured and with debilitation and diminution of resistance by colds, fatigue and so forth, exacerbation of the smoldering infection commonly occurs and "acute pyelitis" develops all over again. Such flare-ups punctuate the careers of countless individuals and notably children who recurrently suffer acute and often severe attacks of urinary infection—usually ill-designated as 'pyelitis'—and in whom the indication of recovery from the acute episode is too often based on a negative routine urinalysis report from a commercial laboratory represented by the corner drug store agency. In most of these cases there is likely to be both persisting bacteriuria and unrecognized urinary obstruction, these factors are of paramount importance in the pathogenesis of urinary infection as discussed in the preceding paragraph. Pathologically, the usual renal lesion in so-called "pyelitis" is a diffuse interstitial suppurative nephritis in which the parenchymal involvement far outweighs in importance the pelvic changes.

**Chemotherapy**—In the chemotherapeutic attack on urinary infection, the functional capacity of the kidneys assumes prime importance, and of scarcely less concern are the reaction of the urine and known intolerance of the patient to any of the urinary antiseptics. Many patients manifest great selectivity in drug tolerance especially as concerns the sulfonamides. In one of my patients, a gentleman of 75 years, as little as 5 grains of methenamine produce marked hematuria and vesical irritability. In another elderly man 20 grains of sulfanilamide precipitated an acute hemolytic crisis which was nearly fatal. Unfortunately the same drug will not eradicate the same type of organism in every individual, but doubtless the usual explanation here is the existence of unrecognized obstruction and/or urinary stasis in the unresponsive patient. Sometimes the selection of the successful drug will be by trial and error, changing until a medication is found which is well tolerated in effective amounts.

Methenamine (urotropin), ketogenic diet, or mandelic acid therapy may be employed when the renal function is good and a urinary acidity below pH 5.5 can be maintained.

**Methenamine**—Methenamine has lost its popularity since the introduction of newer antiseptics but still has a place when employed in the absence of urinary obstruction and in much larger dosage than commonly given. It is of value when the patient cannot take mandelic acid or sulfonamide compounds. The average daily dose in children is 2 grains per pound of body weight and in adults 1 grain per pound of body weight. Sufficient acidulant, preferably enteric-coated tablets of

ammonium chloride, must be co-administered to maintain the urinary acidity below pH 5.5. A sufficiently accurate estimation of the hydrogen ion concentration of the urine can be made in a few seconds by the use of nitrazine paper and the accompanying color chart (Squibb) obtainable at most drug stores.

Treatment of urinary infections by *ketogenic diet* therapy has been largely replaced by the use of mandelic acid or sulfonamide compounds.

**Mandelic Acid**—Mandelic acid is particularly effective against gram-negative bacillary infections with the exception of *Bacillus proteus*, here the intense urinary alkalinity caused by the ammoniogenic *Proteus vulgaris* usually defies effective acidulation (see tabulation). Yet the drug is essentially specific against *Streptococcus faecalis* and will be used most often when this organism causes the urinary infection. Mandelic acid is usually administered as the calcium or ammonium salt, as the elixir, or the syrup, and to be effective must be given in large doses and with sufficient acidulant (preferably enteric-coated) ammonium chloride tablets to render the urine more acid than pH 5.5. Most failures in mandelic acid therapy result from inadequate dosage and failure properly to acidulate the urine. An alkaline intake (sodium bicarbonate, milk of magnesia, citrus drinks and fruits, and the like) is to be strenuously avoided during the medication period. The dose of mandelic acid in adults is 10 to 14 gm per day and for children the dose will vary between 0.3 and 0.5 gm per kilogram body weight according to age and digestive (nutritional) factors. Excepting in the combat of *Streptococcus faecalis* infection, and because of the ease with which acidosis is produced in the young, sulfonamides will be largely employed when the patient is an infant or young child.

**Sulfonamides**—Sulfathiazole and sulfadiazine merit the chief consideration as urinary antiseptics today. Sulfathiazole is particularly effective against *Staphylococcus aureus* and *albus*, colon bacilli and *Streptococcus faecalis*, and this action is favored by acid urine which, unfortunately, predisposes to the formation of and urinary tubular obstruction by acetylated sulfathiazole crystals. The dose of sulfathiazole and sulfadiazine in children is 0.25 gm per kilogram of body weight, and in adults an initial dose of 4 gm per day (for two or three days), then 2 gm per day for six days. An equal amount of sodium bicarbonate is given to alkalinize the urine to prevent intratubular deposit of acetylated sulfonamide crystals. During sulfathiazole or sulfadiazine therapy in adults, a daily excretion of at least 1000 cc must be maintained, preferably 1500 cc, and any less excretion with a twenty-four-hour intake of at least 2500 cc suggests renal injury by the drug or crystalline urinary obstruction especially in the renal tubules. Renal or ureteral pain and hematuria also suggest complicating crystallization and unless, with the drug stopped, renal excretion increases in twenty-four hours, ureteral catheterization and

ureteropelvic lavage to eliminate obstruction by crystal deposit should always be considered and in some cases is imperative. Delay in this has accounted for many deaths. In a patient of ours with sulfathiazole anuria and uremia, the entire upper urinary tract on each side was so filled with and occluded by crystals that it became necessary to perform ureteropyelostomy to establish renal drainage.

Sodium sulfathiazole can be administered intravenously in high dilution (1:500) as an infusion.

Sulfadiazine is especially effective against the colon bacillus, proteus bacillus, most streptococci, less so against staphylococci, and produces untoward reaction in fewer patients than do the other sulfanomides (10 to 15 per cent). The dose and special considerations of its administration have been given in the preceding paragraphs. Sodium sulfadiazine can be given intravenously in the same manner as indicated for sodium sulfathiazole.

Sulfanilamide, sulfapyridine, sulfamerazine, sulfacetimide and succinylsulfathiazole have not proved as satisfactory for general clinical use as sulfathiazole and sulfadiazine. Sulfaguanidine is but slightly excreted through the kidney and is used only for its bacteriostatic effect on intestinal flora.

*Chemotherapy in Acute Urinary Infection*—The chosen drug is administered for seven or eight days unless unfavorable reaction to it develops. After a week of medication a rest of three or four days is given at the end of which time an aseptically collected specimen of urine is examined. If infection persists, the therapeutic course is repeated perhaps with a change of medication, and a similar bacteriologic recheck is made. If there is still infection after two or three weeks of such periods of intensive chemotherapy a complete urologic examination is indicated which is likely to reveal obstruction or, in some instances, surgical renal pathology which must receive appropriate instrumental or operative therapy.

*Chemotherapy in Chronic Urinary Infection*—If favorable response to the bacteriologically indicated chemotherapy is not achieved in four weeks of intensive treatment, a complete urologic examination is indicated and will usually demonstrate uropathology to be treated by combined instrumental and chemotherapy or combined surgical treatment and urinary antiseptics.

When the patient—infant or adult—clinically manifests persistent hyperacute urinary infection (renal) after four to six days of intensive medical therapy, a complete urologic examination is indicated, infected hydronephrosis, fulminating massive or focal renal suppuration, perinephritis, perinephritic abscess, pyonephrosis, or other grave surgical condition is likely to be revealed. Here treatment is often operative together with chemotherapy plus blood transfusions.

*Neocarsphenamine*—Neocarsphenamine has been of considerable value in the past in the combat of *Staphylococcus aureus* urinary infec-

tions, especially as persistent bacteriuria. Today this use of the drug has been replaced by penicillin, the administration of which is far safer, and the therapeutic results obtained with it in the staphylococcal and most diplococcal infections are more immediately dramatic.

*Penicillin*—Penicillin has been employed in a limited number of cases of nontuberculous urinary infections and has been phenomenally successful in most patients with streptococcal and staphylococcal pyelonephritis, uncomplicated by colon bacillus infection. In several instances, the penicillin eradicated the gram-positive organisms but had no effect on the gram-negative bacilli. The previous tabulation indicates the bactericidal activity of penicillin. In most adults an intramuscular injection of 25,000 units every three or four hours is given for three or four days. At the end of this time, bacteriologic recheck of the urine will indicate whether further medication—penicillin or sulfonamide or combined therapy—is needed.

#### SUMMARY

In the foregoing paragraphs attention has been directed to the basic considerations in the treatment of nontuberculous urinary infections in patients of all ages, the details of administration of the various urinary antiseptics have not been discussed since full description is usually given on the commercial package. In at least half of the cases of acute urinary infection and in most instances of chronic urinary infection, complicating pathologic changes—notably obstruction—require special consideration and treatment in addition to chemotherapy. In short, in only a third to a fourth of all cases of nontuberculous urinary infection does chemotherapy alone achieve full benefit for the patient. No patient should be discharged as cured of infection until examination of at least two properly collected specimens by culture or microscopically is negative. If this dictum is observed, the incidence of so-called "recurrent pyelitis" will be infinitely reduced and an inestimable amount of renal damage will be prevented.

## PENICILLIN VERSUS SULFONAMIDE THERAPY

LT COLONEL A. ALLEN GOLDBLOOM AND MAJOR EMANUEL H. NICKMAN  
MEDICAL CORPS, ARMY OF THE UNITED STATES

In the late 1930's, when sulfonamide therapy came into general usage the medical profession as well as the general public felt that it would be a panacea for bacterial as well as other infections. Its field of usefulness has now become definitely defined and its capabilities and limitations now generally known. With the advent of penicillin a great wave of enthusiasm for it theoretically swept sulfonamides into disuse. It was felt that penicillin could do anything that the sulfonamides could do and do it more efficiently. Fortunately, the drug was not available at that time except to those who could study its properties under controlled conditions. This has prevented indiscriminate usage with resultant misconceptions and has made for a more rapid crystallization of thought with regard to its field of usefulness.

These studies have shown that

- 1 The antibacterial activity of sulfonamides and penicillin are similar in effect against gram-positive and certain gram-negative organisms, in general penicillin being by far the more efficient and the less toxic.

- 2 Certain specific infections are benefited by sulfonamides and not by penicillin, and vice versa.

- 3 When there are like indications for sulfonamides and penicillin, one may be substituted for the other under the following circumstances (a) drug-resistance or drug fastness, (b) nonavailability of the agent of choice, (c) in the presence of contraindications to the agent of choice.

- 4 Penicillin and sulfonamides, under certain circumstances, may be synergistic in action, as is suggested by recent investigations with animals which have demonstrated that when sulfonamides and penicillin are given together the protective effect is greater than when each is given separately.<sup>1</sup>

Many investigators have compared the therapeutic response of penicillin and sulfa products. They have almost invariably reported the superiority of the former both in vitro and in vivo. Fleming<sup>2,3,4</sup> showed that crude penicillin was four times as efficient a bacteriostatic as sulfathiazole and twenty times more powerful than sulfapyridine when used against *Streptococcus pyogenes* and *Staphylococcus aureus* in human blood. Hobby, Meyer and Chaffee<sup>5</sup> working with hemolytic streptococci in broth cultures also reported penicillin to have a greater

---

From the Medical Service, Station Hospital, Camp Kilmer, New Jersey. John M. Tamraz, Colonel, Commanding.



antibacterial effect than sulfathiazole. Both were bacteriostatic, but penicillin alone caused a reduction in the number of organisms. Rosenberg and Arling<sup>6</sup> reported recovery in seventy out of seventy-one cases of meningitis caused by the meningococcus, *Streptococcus hemolyticus*, *Streptococcus viridans* and pneumococcus treated with penicillin. This series represents a better result than is ordinarily obtained with sulfonamide therapy, however, our own experience indicates that excellent results can be obtained with the latter alone. In an as yet unpublished group of fifty-eight consecutive cases of meningococcal meningitis treated only with sulfonamides complete recovery occurred in every case.<sup>7</sup>

Abraham and his co-workers summarize the advantages of penicillin over sulfonamides as follows: (1) It is influenced only slightly by the number of bacteria to be inhibited. (2) It is not antagonized by hydrolytic break-down products or pus. (3) It combines low toxicity to cells with powerful bacteriostatic action. (4) Its action is stronger.

In spite of the advantages of penicillin over sulfonamides as the therapeutic agent of choice in those diseases in which either could be used, certain practical considerations present themselves. These are: (1) the present greater availability and lower cost of sulfonamides, and (2) the ability to administer sulfonamides by mouth as compared to penicillin, which must be given parenterally. While these considerations by no means preclude the practical employment of penicillin, they do limit its usage.

We feel that at present and until it is readily available penicillin will find its greater application in life-endangering infections, in those conditions which are sulfa-resistant, and where the use of sulfonamides is contraindicated.

#### CASE REPORTS

A series of eight cases, all of which were life endangering, is presented in the accompanying table. In the first and second cases penicillin alone was used because sulfonamides were contraindicated. Cases III to VI inclusive were sulfa-resistant, penicillin being administered secondarily. Cases VII and VIII represent failure of both sulfa and penicillin therapy.

**CASE I—Rheumatic Fever, Bronchopneumonia**—This white man, aged 26, was in good health until a few days before he was admitted to the hospital on March 12, 1944, when he became ill with generalized malaise and fever. On the day after admission he developed a generalized erythema associated with arthralgia of the lower extremities. Arthralgia became migratory, low grade fever persisted, endocardial and myocardial changes were noted. A diagnosis of rheumatic fever was made on the basis of the above findings.

Seven weeks after the onset of rheumatic fever his temperature suddenly became septic in type and rose to 104.4° F. Marked orthopnea was present. Physical examination and x-rays indicated a bilateral basilar bronchopneumonia. Sputum organisms were predominantly pneumococci. He was given penicillin,

SUMMARY OF CASES TREATED WITH PENICILLIN (SODIUM SALT)

Case	Age	Diagnosis	Infecting Organism	Total Dosage in Units	Method of Administration	Days Treated	Result	Comment
I	76	Rheumatic fever Pneumonia, broncho-	Diplococcus pneumoniae	480,000	20,000 u q3h I.M.	4	Failure Recovery	Sulfonamides not given, contraindicated No reactions to penicillin.
II	37	Nephritis, acute glomerulonephritis	Diplococcus pneumoniae	100,000	10,000 u. q3h I.M.	1½	Recovery Recovery	Sulfonamides not given, contraindicated. No reactions to penicillin
III	37	Pneumonia, lobar Septicemia	Strep hemolyticus	1,161,500	20,000 u q3h I.M.	6	Recovery	Sulfonamides ineffective.
IV	38	Endocarditis, sub-acute bacterial	Strep viridans	2,545,000	10,000 to 20,000 u q3h I.V. 10,000 to 20,000 u q3h I.M.	7	Blood cultures negative Partial recovery	No reactions to penicillin. Sulfonamides ineffective
V	22	Cellulitis	Staph aureus	745,000	20,000 u q3h I.M.	4	Recovery	Sulfonamides ineffective.
VI	23	Meningitis	Diplococcus pneumoniae	1,295,000	Intrathecal, I.V., I.M.	8	Recovery	No reactions to penicillin Initial intrathecal dose of penicillin 50,000 u., then 10,000 to 20,000 u daily I.M. injections of 25,000 to 10,000 u q3h Only 2 I.V. injections given.
VII	34	Brucellosis	Brucella melitensis (?)	1,000,000	20,000 u q3h I.M.	6	Failure	Skin test with Brucella antigen strongly positive in all dilutions. Penicillin and sulfonamides ineffective. No reactions to penicillin
VIII	21	Tuberculosis, pulmonary	Micobact. tuberculosis	300,000	15,000 u q4h	3	Failure	Penicillin and sulfonamides ineffective No reactions to penicillin

20,000 units every three hours intramuscularly for four days (total 480,000 units) Arrest of the pneumonic process ensued Fever dropped by lysis to normal within seventy-two hours

Cardiac and joint signs and symptoms were unaffected by the penicillin Subsequently, these improved under salicylate and digitalis therapy

*CASE II—Acute Glomerulonephritis, Lobar Pneumonia*—This patient, a white man, aged 37, was admitted to Station Hospital, complaining of coryza, nausea, vomiting and painful and diminished urination He gave a history of prolonged exposure to inclement weather several days before admission

Signs of acute glomerulonephritis and congestive heart failure were manifest There was almost complete anuria, albuminuria and hematuria, enlarged and tender liver, peripheral edema, cardiac dilatation and a mitral murmur heard at the base of the heart and not transmitted Almost simultaneously physical examination showed signs of lobar pneumonia This was confirmed by x-ray and by the presence of innumerable pneumococci in his sputum

In view of the patient's anuria, sulfa therapy was considered to be contraindicated, and a course of intramuscular penicillin, 10,000 units every three hours, was instituted Pneumonic phenomena and fever subsided within thirty-six hours Alarming kidney and cardiac signs also subsided within this period, but for six weeks thereafter there was a slightly elevated pulse, barely palpable tender liver and a nontransmitted mitral murmur Penicillin, of which a total of 100,000 units was given, was discontinued immediately after the acute symptoms had subsided

Physical examination two months after admission showed no heart or kidney damage. No therapy other than penicillin and supportive measures was used in this case

In Case I the patient had a severe rheumatic fever with myocardial and valvular changes When he developed a complicating bronchopneumonia with signs of acute decompensation, it was felt that he would not survive the double infection Sulfonamide treatment of the pneumonia was not given because of its reported ill effects in acute rheumatic fever Penicillin proved completely effective in curing the pneumonia but had no effect whatsoever upon the course of the rheumatic infection

In Case II we were confronted with a patient with acute cardio-renal failure as well as lobar pneumonia It was obvious that sulfonamide therapy could not be employed to treat the pneumonia because of the anuria Penicillin was promptly started with very satisfactory results, not only in the pneumonia for which it was primarily intended but also in the acute glomerulonephritis The acute severe signs of the latter were under control within seventy-two hours The beneficial effect of penicillin in the latter instance was probably due to kidney excretion of penicillin of higher antibacterial titer as reported by numerous investigators <sup>8, 9, 10</sup>

While the satisfactory response of pneumococcal pneumonias to sulfonamides is well known, the two cases presented illustrate the importance of penicillin when the use of the former is contraindicated

*CASE III—Septicemia*—A male patient, aged 37, was admitted to the hospital complaining of chills and fever Physical examination was negative except for a

moderately reddened pharynx and poor oral hygiene. Dental x rays showed root abscesses around four teeth. Blood culture was positive for *Streptococcus hemolyticus*, Type 17.

It was deemed advisable to begin sulfadiazine therapy before attempting the removal of the abscessed teeth. The drug was given in two courses, one of eleven days averaging 6 gm of sulfadiazine daily, and again, after an interval of five days, in a second course of nine days, averaging 5 gm daily.

In spite of the above medication two positive blood cultures were obtained during the course of treatment, nor did the sulfadiazine eliminate the fever which continued to be of an irregular low grade type with occasional septic exacerbations fluctuating between 98 and 105.2 F. The patient was weak and cachectic and had a yellow waxy pallor.

On May 29 sulfadiazine was discontinued and penicillin started. The patient was given 20,000 units intramuscularly every three hours for six days and a diminishing amount for three additional days. A total of 1,161,500 units was given. A remarkable improvement was noted within twenty-four hours after starting penicillin; the patient expressed a feeling of vitality and well-being, was hungry and cheerful, his temperature was normal, and blood culture was negative. Improvement continued uninterruptedly until his discharge.

On June 1 four abscessed teeth were extracted. No clinical or febrile reaction ensued. All blood cultures after May 29 were negative.

The patient was discharged cured on June 26, 1944.

This patient was given sulfadiazine over a prolonged period during which he showed equivocal clinical and no bacteriologic response to treatment. Under penicillin, recovery was dramatically prompt. Herrell<sup>11</sup> feels that sulfonamide compounds are so effective against hemolytic streptococcal infections as to make it unnecessary to use penicillin except occasionally. Our experience with this case, as well as the experience of others,<sup>12, 13</sup> makes it evident that, when sulfonamide-fast infections of this type occur, penicillin is the therapeutic measure of choice. The euphoria and improvement in appetite which were noted in this case were seen also in other of our patients treated with penicillin. Florey and Florey<sup>14</sup> have made a similar observation.

**CASE IV.—Subacute Bacterial Endocarditis.**—A white man, aged 38, was admitted on March 1, 1944. His history was negative except for a questionable heart murmur in 1923. About three weeks before admission he began having chills and fever which were of daily occurrence for two weeks before he applied for hospitalization. He had no apparent source of infection other than a mild rhinitis.

A physical examination revealed the patient to be acutely ill, pale and sweating profusely. No petechiae or other evidence of embolic phenomena were present. There was no splenic or hepatic enlargement. A long blowing systolic murmur was heard in the mitral area and transmitted to the left axilla. This murmur was apparently of recent origin, since previous routine examinations over a period of one year indicated no cardiac pathology. The blood pressure was 100/70, the temperature 98.6 to 101.6 F. Three blood cultures taken between March 1 and 6 were positive for *Streptococcus viridans*.

Beginning March 6 penicillin was given both intravenously and intramuscularly for seven days for a total of 2,545,000 units.

Upon completion of penicillin therapy the temperature was normal, blood

culture was negative, and the patient was asymptomatic. Cardiac signs were essentially unchanged except that the mitral murmur could be heard in diastole as well as systole. Hospitalization was continued for one month, during which time blood cultures were negative and temperature remained normal, however, his blood sedimentation rate remained high (125 mm per hr) and the mitral murmur was still present on April 12, 1944, when he was transferred to a convalescent hospital.

Seven months after the onset of his illness the patient was still alive and had sterile blood cultures.

There has been no uniformity in the reported results of penicillin therapy in subacute bacterial endocarditis. In vitro studies<sup>15</sup> indicate that *Streptococcus viridans* is inhibited or destroyed by penicillin, but in concentrations 200 to 1000 times as great as is required for *Streptococcus hemolyticus*. Loewe and his associates<sup>16</sup> have reported seven cases treated successfully with penicillin and heparin, although they claim no permanency of cure. Keefer<sup>17</sup> states that of fifty-five cases reported to the Committee on Chemotherapeutic and Other Agents of the National Research Council only three patients are alive after one year of study. Others<sup>11, 14, 18, 19</sup> have reported temporary sterilization of the blood or absolute failure.

Further study is obviously required to crystallize opinion with regard to the efficacy of penicillin in this disease. It is possible that high penicillin dosage, as was used in our case and as suggested by the in vitro studies mentioned above, may prove to be the answer to the problem.

**CASE V—Cellulitis.**—A 22 year old white soldier was admitted to the hospital August 15, 1944, complaining of headache, nausea and pain in the right leg.

He gave no history of recent acute illness, chronic disease, or residence in the tropics. He stated that on the night before admission he had been scratching his right shin in an area which had been hit by a dummy hand grenade one month prior to admission.

Examination revealed an acutely ill and moderately disoriented individual. There was a furuncle on the anterior aspect of the lower one-third of the right leg 1 cm in diameter surrounded by a zone of erythematous induration 8 cm in diameter, tender to touch. Femoral and inguinal lymph nodes on the right side were moderately enlarged and painful. No lymphangitis was present. On admission, the patient's temperature was 102° F., pulse 92 and respiration 22.

Sodium sulfadiazine, 5 gm., and 1000 cc of 5 per cent glucose in saline were given intravenously immediately. However, the patient's condition became progressively and rapidly worse with lethargy, restlessness and increase in size of the lesion, the surrounding erythematous induration and the regional lymphadenopathy. Sulfadiazine was discontinued and penicillin substituted.

Under penicillin therapy the patient's temperature dropped from 102.2° to 98.8° F within ten hours and remained within normal limits thereafter. Pain and local pathology remained stationary for two days, but the patient's systemic symptoms were much improved. On the third day, there was a gradual lessening of the local and regional pathologic processes. Improvement continued until on discharge, seven days after admission, the lesion was healed and regional lymphadenopathy was absent. This patient received 20,000 units of penicillin intramuscularly every three hours over a period of four days for a total of 745,000 units.

The remarkably rapid response of this patient to penicillin is in accord with innumerable reports of the successful treatment of *Staphylococcus aureus* infections either with or without bacteremia. It has been noted<sup>15-20</sup> that staphylococci are more resistant to penicillin than hemolytic streptococci and that a larger dosage may be indicated in the case of the former. Lyons,<sup>21</sup> who has a wide experience with penicillin in surgical infections, voices the belief that adequate therapeutic dosage must be given in all cases treated with penicillin, particularly the staphylococcal infections. Unfortunately, the accumulated knowledge of those who have had clinical experience with penicillin is at present insufficient to determine what is adequate and what is inadequate dosage. Further work is necessary in this field before specific criteria can be established for rules of dosage.

**CASE VI.—Meningitis.**—This patient, a white man, aged 23, was admitted on Jan. 5, 1944, in a moribund condition. He was unconscious and cyanotic and had marked nuchal rigidity. Loud bubbling rhonchi could be heard. Several generalized clonic convulsions took place within the first hour of hospitalization.

Subsequently obtained history indicated that he had been injured in a motor cycle accident two and one-half months before admission while on duty in Africa. At that time he sustained a compound comminuted fracture of the right frontal bone and cribriform plate, a simple comminuted fracture of the nasal bone and paralysis of the right third cranial nerve. Following the accident he continued to drain a thick clear fluid from the right nostril. After treatment in various hospitals for two and one-half months he was granted a sick furlough. Three days before his present admission he began having right frontal headaches and dizzy spells to which he paid little heed, as he attributed them to his injury. These symptoms and progressive weakness persisted for two days. On the morning of the third day he was found in bed in an unconscious state.

Physical examination of the patient on admission showed profound stupor, nuchal rigidity, positive Kernig's, Brudzinski and Babinski signs, inexhaustible bilateral ankle clonus and exaggeration of all deep reflexes. There was moderate peripheral cyanosis, innumerable petechiae on trunk and extremities and herpes labialis. The heart was enlarged, the heart sounds of poor quality, the pulse was unperceptible and pulmonary edema was present.

Spinal fluid examination showed *Diplococcus pneumoniae*, Type 14 in abundance.

Sodium sulfadiazine intravenously was given for six hours. During this period all physical signs became worse. Opisthotonos was present, cyanosis became generalized, pulmonary edema became worse with the appearance of abundant frothy mucus in the patient's mouth, and convulsions increased in frequency. It was felt that exitus was imminent.

Penicillin was started at this time, 50,000 units being given intrathecally at once. This was followed by intravenous and intramuscular injections of 25,000 units each. Within twelve hours a gradual improvement in the clinical picture took place. Pulmonary signs, cyanosis, opisthotonos and convulsions were absent, the patient was quieter and the temperature which had been 105° F. on admission was now 100.4° F.

Intrathecal penicillin was administered once daily for four additional days in 10,000 to 20,000 unit dosages. Intramuscular penicillin was continued in gradually descending dosages of from 25,000 to 10,000 units every three hours for eight days. The total dosage of penicillin was 1,295,000 units.

The patient regained consciousness on the third hospital day. Improvement was slow but uninterrupted. Pneumococci were absent from the spinal fluid after the sixth day of penicillin therapy.

X-ray examination showed clouding of all paranasal sinuses on the right side. These were treated locally during convalescence. No nasal discharge was present on completion of treatment.

The patient was discharged cured on the seventieth day of hospitalization. There were no sequelae.

This case is illustrative of the life-saving properties of penicillin even when given to a moribund patient. Until penicillin therapy was administered no hope was held for his recovery, in fact, it was felt at the time (January 1944) that the meager supply of penicillin available was being wasted. However, after 200,000 units had been given, its use was rewarded by definite clinical improvement. The initial intrathecal injection of 50,000 units was felt to be warranted despite the fact that dosages higher than 10,000 units were thought to cause reactions.<sup>22, 23, 24</sup> No ill effects were observed in our case. Priest<sup>25</sup> has reported having used intrathecal dosages as high as 40,000 units without significant reactions. Evans<sup>26</sup> reported cure of a case of *Staphylococcus albus* meningitis in which 25,000 units were given once daily for six days without producing pleocytosis or other toxic manifestations.

Daily intrathecal injections in our case were supplemented by intravenous and intramuscular injections of penicillin. Early reports of the ineffectiveness of intravenous and intramuscular administration in meningitic infections were based upon the finding that in normal subjects penicillin does not traverse the blood-brain barrier in significant amounts. However, it has been shown that, when the meninges are inflamed, appreciable absorption does occur,<sup>22</sup> making these routes valuable supplements to intrathecal administration.

**CASE VII—Brucellosis**—A white woman, aged 34 years, was admitted May 7, 1944, complaining of fever, malaise, vague generalized pains, marked weakness, chronic nausea, occasional fainting spells, and transitory cyanosis of the upper and lower extremities. This was her fourth hospitalization within a period of seven months.

Her past history was essentially negative except for the ingestion of raw goat's milk in August, 1943. It was shortly after this that she began to feel badly.

Skin tests with *Brucella* antigen were positive in all dilutions. Her opsonic index was indicative of a past *Brucella* infection or chronic brucellosis.

Physical examination and special studies of heart, lungs, gastrointestinal tract, gallbladder and genitourinary tract were essentially negative. X-ray of the dorsolumbar spine showed slight erosion of several vertebrae. Her temperature fluctuated between 98.6° and 100.2° F.

Various types of treatment had been tried prior to her present hospitalization, including the use of Huddleson's vaccine. She noticed no benefit from anything except sulfadiazine, which caused a temporary cessation of symptoms during febrile periods. Symptoms returned upon withdrawal of the drug.

Penicillin therapy was instituted, the patient receiving 20,000 units intramuscularly every three hours for six days. The total dosage was 1,000,000 units. No

improvement was noted either during or following penicillin. The patient was discharged unimproved.

Despite reports of failure in *Brucella* infections, the use of penicillin was felt justified in this case because all other therapeutic measures had been of no avail in controlling the pain and severe debilitating symptoms which this patient had experienced for seven months.

**CASE VIII—Pulmonary Tuberculosis**—A man aged 21 of Mexican ancestry and native of California, was admitted November 2 1943. He became ill on a troop train three days before admission, with headache, cough and hemoptysis, estimated at 200 cc. He gave no previous history of night sweats, loss of weight, weakness, anorexia, dyspnea, or hemoptysis. He had been well since birth. There were no known tuberculous contacts in his family or among his associates.

Examination on admission revealed flatness, crackling rales, tactile and vocal fremitus in the lower lobes of both lungs. These findings persisted throughout his hospitalization. X rays were indicative of a bronchopneumonia of both lower lobes. Apices were clear.

The patient's course was very stormy with periods of dyspnea which necessitated oxygen therapy, numerous hemoptyses varying in amount from 30 to 400 cc., constant and severe cough productive of small quantities of mucopurulent sputum, and septic temperature fluctuating between 97° and 104.6° F.

During the first two weeks following admission it was felt that the patient had an overwhelming streptococcal bronchopneumonia as suggested by several smears of sputum containing innumerable streptococci. Cultures at this time were negative or uncompleted. Sulfadiazine was administered during this period without benefit. Daily examinations for tubercle bacilli were negative for nine days. Penicillin therapy was started on the ninth day in the amount of 15,000 units intramuscularly every four hours and continued for three days. A total of 300,000 units was given.

Treatment was suspended with the finding of innumerable tubercle bacilli in the tenth and eleventh sputum specimens, since it has been well established that tuberculosis does not respond favorably to penicillin.

Penicillin therapy had no apparent influence on the course of this patient's illness except for the coincidental cessation of hemoptysis and diminution in dyspnea. Physical signs, x ray findings and fever were unchanged up to twenty-one days after penicillin was discontinued.

Little need be said with regard to the two preceding cases. Neither sulfonamides nor penicillin were of any benefit in controlling the infections, both of which were due to gram negative bacilli. Numerous *in vitro* and *in vivo* studies have conclusively shown that penicillin has no effect upon this type of organism. Recent experimental investigations with flavicin,<sup>27</sup> streptothricin<sup>28</sup> and other antibiotics, however, suggest that the practical treatment of gram negative infections with chemotherapeutic agents is a distinct possibility in the not too distant future.

#### SUMMARY AND CONCLUSIONS

The foregoing study discusses the relative merits of penicillin and sulfonamides in the treatment of bacterial infections and presents eight cases, all of them life-endangering, treated with penicillin. Penicillin



was remarkably successful in all of the cases in which gram-positive organisms were the etiologic agents *Diplococcus pneumoniae*, *Streptococcus hemolyticus* and *Staphylococcus aureus* were the infecting bacteria in this group

Sterilization of the blood by penicillin was effected in one case of *Streptococcus viridans* infection

Dosage and method of administration was principally by intramuscular injections of 10,000 to 20,000 units at three hour intervals, which we believe to be the most practical method for general use The patient with pneumococcal meningitis received an initial intrathecal instillation of 50,000 units, followed by daily intrathecal dosages of 10,000 to 20,000 units supplemented by intramuscular injections of 10,000 to 25,000 units every three hours Intrathecal injection is essential in meningitic infections treated with penicillin Other methods of administration have only supplementary value

No toxic reactions were encountered in any of the cases presented

We feel that at present, and until it is readily available, penicillin will find its greatest application in life-endangering infections, in those conditions which are sulfonamide resistant, and in those conditions in which the use of sulfonamides is contraindicated

#### BIBLIOGRAPHY

- 1 Ungar, J Synergistic Effect of Para-aminobenzoic Acid and Sulfapyridine on Penicillin. *Nature*, London, 152,245-246 (Aug 28) 1943
- 2 Fleming, A Antiseptics in War-time Surgery *Pharmaceut. J.*, 145 162 (Nov 23) 1940, 145 172 (Nov 30) 1940
- 3 Fleming, A Discussion on Chemotherapy and Wound Infection *Proc Roy Soc Med.*, 34 342 (April) 1941
- 4 Fleming, A In-Vitro Tests of Penicillin Potency *Lancet*, 1 732-733 (June 20) 1942
- 5 Hobby, G L, Meyer, K and Chaffee, E. Observations on the Mechanism of Action of Penicillin *Proc Soc Exper Biol & Med.*, 50 281-285 (June) 1942
- 6 Rosenberg, D H and Arling, P A Penicillin in the Treatment of Meningitis *J.A.M.A.*, 125 1011-1017 (Aug 12) 1944
- 7 Goldbloom, A. A and Nickman, E. H Unpublished data in 58 successive nonfatal cases of meningococcal meningitis treated with sulfonamides
- 8 Herrell, W E, Nichols, D R and Heilman, D H Penicillin Its Usefulness, Limitations, Diffusion and Detection *J.A.M.A.*, 125 1003-11 (Aug 12) 1944
- 9 Rammelkamp, C H and Bradley, S E. Excretion of Penicillin in Man *Proc. Soc Exper Biol & Med.*, 53 30-32 (May) 1943
- 10 Rammelkamp, C H and Keefer, C S The Absorption, Excretion and Distribution of Penicillin *J Clin Investigation*, 22 425-437 (May) 1943
- 11 Herrell, W E. The Clinical Use of Penicillin, an Antibacterial Agent of Biologic Origin, *J.A.M.A.*, 124 622-627 (March 4) 1944
- 12 Keefer, C. S., Chairman, Blake, F G, Marshall, E K., Jr, Lockwood, J S and Wood, W B., Jr Penicillin in the Treatment of Infections, A Report of 500 Cases *J.A.M.A.*, 122 1217-1224 (Aug 28) 1943
- 13 Richards, A N., Chairman Penicillin Statement released by the Committee on Medical Research *J.A.M.A.*, 122 235 (May 22) 1943

- 14 Florey M E. and Florey, H W General and Local Administration of Penicillin *Lancet*, 1 387-397 (March 27) 1943
- 15 Robinson H J Toxicity and Efficacy of Penicillin. *J Pharmacol & Exper Therap.*, 77 70-79 (Jan) 1943
- 16 Loewe, L., Rosenblatt, P., Greene, H J and Russell, M Combined Penicillin and Heparin Therapy of Subacute Bacterial Endocarditis Report of Seven Consecutive Successfully Treated Patients. *J.A.M.A.*, 124 144-149 (Jan. 15) 1944
- 17 Keefer C. S Discussion, Symposium on Antibiotic Agents *J.A.M.A.*, 124 636-637 (March 4) 1944
18. Dawson, M H. and Hobby G L. The Clinical Use of Penicillin Observations in One Hundred Cases. *J.A.M.A.*, 124 611-622 (March 4) 1944
- 19 Herrell, W E. Further Observations on the Clinical Use of Penicillin. *Proc. Staff Meet., Mayo Clin.*, 18 65-76 (March 10) 1943
- 20 Blake, F G and Craige, B., Jr Penicillin in Suppurative Disease of the Lungs *Yale J Biol & Med.*, 15 507-516 (Jan.) 1943
- 21 Lyons C. Penicillin Therapy of Surgical Infections in the U S Army *J.A.M.A.*, 123 1007-1018 (Dec. 18) 1943
- 22 Rammekamp C. H and Keefer C. S. The Absorption, Excretion and Toxicity of Penicillin Administered by Intrathecal Injection. *Am J M Sc.*, 205 342-350 (March) 1943
- 23 Pilcher C. and Meacham, W F The Chemotherapy of Intracranial Infections. III. The Treatment of Experimental Staphylococcic Meningitis with Intrathecal Administration of Penicillin. *J.A.M.A.*, 123 330-332 (Oct. 9) 1943
- 24 Barker L. F Gradenigo Syndrome Complicated by Pneumococcic Meningitis Recovery after Intensive Treatment with Penicillin and Sulfadiazine. *Am J M Sc.*, 206 701-703 (Dec) 1943
- 25 Priest, W S. Discussion, Symposium on Antibiotic Agents. *J.A.M.A.*, 124 637 (March 4) 1944
26. Evans, A. L. The Treatment of Intracranial Infections with Penicillin Report of Three Cases. *J.A.M.A.*, 124 641-643 (March 4) 1944
- 27 Bush, M T and Goth, A. Flavicin An Antibacterial Substance Produced by an *Aspergillus Flavus*. *J Pharmacol & Exper Therap.*, 78 164-169 (June) 1943
28. Wakaman, S A. et al Editorial Streptothricin *J.A.M.A.*, 126 103 (Sept. 9) 1944

# THE USE OF ELECTROCARDIOGRAMS IN MEDICINE

HAROLD J STEWART, MD, FACP\*

NUMEROUS papers have been written about electrocardiographic changes in many phases of clinical and experimental medicine and there are many textbooks dealing with the various waves of the electrocardiogram and alterations of them by various diseases which affect the heart directly or remotely. There is need however, for the definition of the use of the electrocardiogram—the recognition of situations in clinical medicine in which it may be expected to yield decisive information of its own or information that will contribute to the clinical picture, in short the integration of the electrocardiogram into clinical medicine. The electrocardiographic interpretation should be considered in association with clinical and other laboratory data. One who reads and interprets electrocardiograms should be a clinician and interested in not only clinical cardiology, but all clinical medicine. The use of electrocardiograms should serve as a check upon the physicians' clinical abilities and contribute to their acuity, rather than to spare them the trouble of careful clinical observations. Especially should this be the case in respect to irregularities of the heart.

Electrocardiograms should be taken under as standard conditions as possible. It is best to have all patients lying down because at later times they may be too sick to sit in a chair, and the two positions might make some differences in the form of the electrocardiogram, for it is known that the position of the body alters the form of the chest lead<sup>1</sup> and of the three standard leads<sup>2</sup>. Moreover, drinking ice water brings about decrease in amplitude of  $T_2$  and negativity of  $T_3$  without altering  $T_1$ <sup>3</sup> and after the ingestion of food the amplitude of T waves may decrease<sup>4</sup>. Recent analysis of large number of electrocardiograms taken on young individuals in whom the physical status was known alters slightly the interpretation of changes which were formerly considered abnormal<sup>5</sup>.

## IRREGULARITIES OF THE HEART

What are the situations in which the electrocardiogram gives information and contributes to understanding of a patient's illness? It is fitting that the irregularities should be mentioned first, not only because in them electrocardiograms usually give information which can be interpreted correctly, but also because historically this was the first

---

From the New York Hospital and the Department of Medicine, Cornell University Medical College, New York City, New York.

\* Associate Professor of Medicine, Cornell University Medical College, Attending Physician, New York Hospital, New York City.



Also it is well to know from the electrocardiographic record that the rhythm is *auricular flutter* because in most instances digitalis is the drug of choice and is more likely to cause reversion to normal rhythm than quinidine. A larger amount may be required than the usual therapeutic one to terminate this rhythm. If success is not achieved by its use, quinidine is occasionally effective.

It is in the other types of paroxysmal tachycardia that exact therapy requires that the rhythm be identified before drugs, such as quinidine and digitalis, are used. namely in *auricular*, *nodal* and *ventricular*

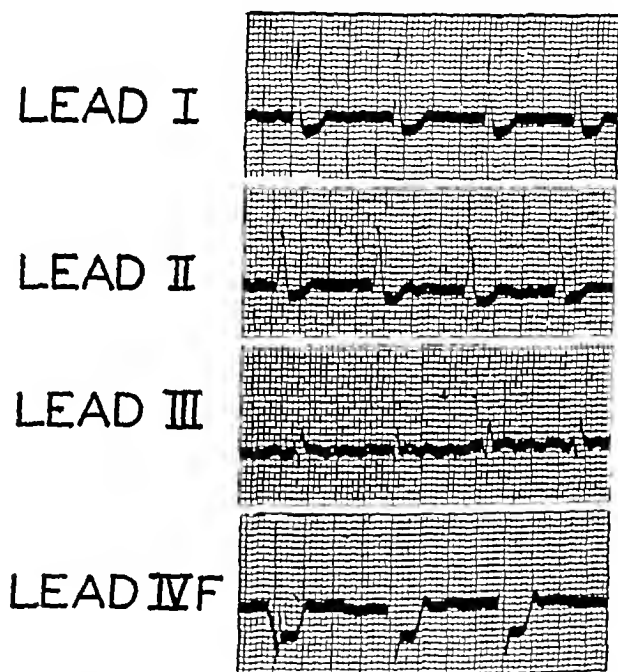


Fig 98—In this figure are reproduced the three standard leads and chest lead IVF of an electrocardiogram exhibiting auricular fibrillation with regular ventricular sequence. In this and in electrocardiograms to follow, standardization was such that one millivolt produced 1 cm deflection of the string. Divisions of the ordinates equal  $10^{-4}$  volts. Divisions of the abscissae equals 0.04 second.

*paroxysmal tachycardias*. In the two supraventricular paroxysmal tachycardias, digitalis is usually the drug of choice and is effective in terminating an attack, but in ventricular paroxysmal tachycardia, digitalis is contraindicated and if used may give rise to ventricular fibrillation and death. On the other hand, in the presence of ventricular paroxysmal tachycardia, the use of quinidine is indicated. Similarly if syncope is due to transient attacks of ventricular fibrillation, the use of quinidine is warranted and digitalis contraindicated. If syncope is associated with complete heart block in the absence of congestive heart failure, there is no occasion to use digitalis but ephedrine (20 to 30

mg t.i.d.), barium chloride (0.3 to 0.6 gm t.i.d.), or adrenalin (1 cc of 1:1000) may be tried. Digitalis does not appear to be contraindicated either in incomplete heart block such as occurs in active rheumatic infection, or in complete heart block, if heart failure requires its use.

In those cases of supraventricular paroxysmal tachycardia in which mechohyl is used (10–25 mg subcutaneously), it is good practice to have the patient connected to the galvanometer, if possible, while the drug is being injected. At any rate, auscultation over the heart should be made continuously. It is perhaps needless to say that atropine should be ready at hand to use if required and that mechohyl should not be used when there is an allergic history.

The electrocardiographic technic is of help in the diagnosis of the *carotid sinus syndrome*. It is our custom to take electrocardiograms during pressures over the right and left carotid sinus when their hypersensitivity is suspected, in order to record the prevailing rhythm. In the vagal type there may occur varying degree of auriculoventricular



Fig 99—In this figure is shown Lead II of the electrocardiogram taken during pressure over a hypersensitive left carotid sinus. Arrows indicate the beginning and end of pressure. There was complete cardiac standstill for 7.4 seconds, during which the patient experienced loss of vision and "black film over the eyes." Blood pressure could not be obtained during asystole.

heart block, or sinus arrest with asystole (Fig 99), during which there is fall in blood pressure and syncope.<sup>9</sup>

From what has been said, the importance of making the exact diagnosis, particularly of the paroxysmal rapid and slow rhythms, is apparent, not only because of the discomfort attendant upon these rhythms but also because congestive heart failure may ensue if the rhythm is not terminated, and, moreover, if the appropriate drug is not used, harm may result. The decreased functional capabilities of the heart during certain rapid rhythms indicate the need for prompt therapy (Fig 100).<sup>10</sup>

In serial electrocardiograms alterations of the T waves have been recorded with restoration of the normal rhythm after paroxysmal tachycardia.<sup>11, 12, 13</sup> If changes are marked and undergo slow regression it appears that myocardial damage must have occurred associated with myocardial ischemia due to the decreased coronary blood supply which no doubt prevailed while the abnormal rhythm was present. It is known that marked decrease in cardiac output is present during paroxysmal tachycardia (Fig 100).<sup>10</sup> Adequate rest should be insti-

tuted in such cases, although the implications and prognosis are quite different from changes occurring with closure of a coronary vessel. When electrocardiographic changes are recorded after paroxysmal

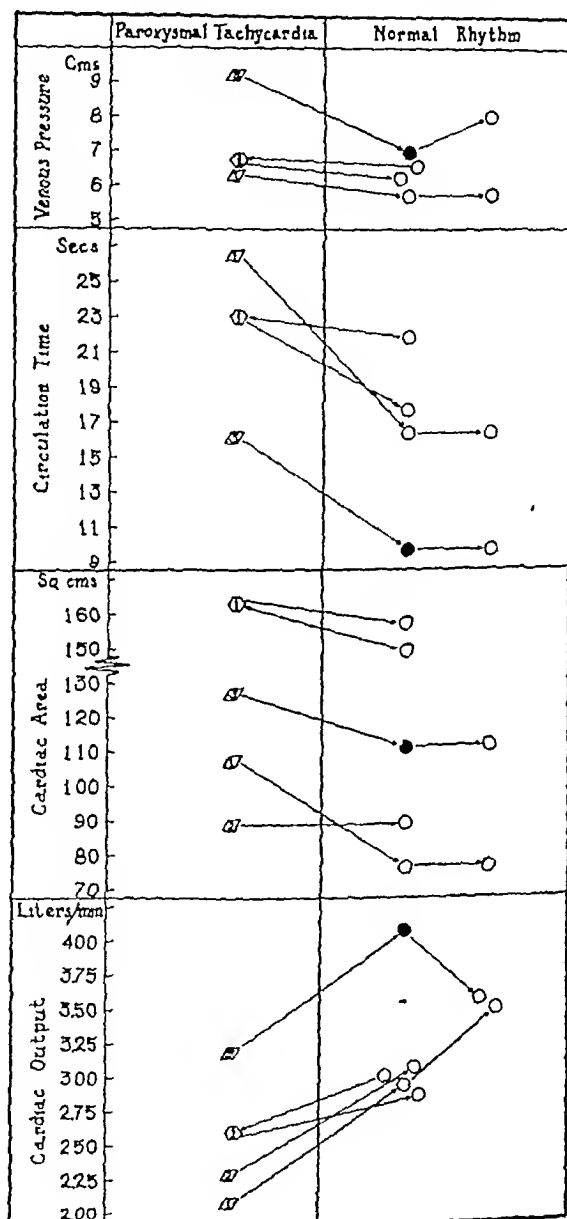


Fig 100.—In this figure is shown the effect of paroxysmal tachycardia on the cardiac output, cardiac size, circulation time and venous pressure, namely decrease in cardiac output, dilatation of the heart, and prolongation of the circulation time (Stewart, H J, Detrick, J E., Crane, N F and Thompson, W P J Clin Investigation, Vol 17)

tachycardia it is important moreover to consider whether the paroxysm might itself have been precipitated by coronary obstruction.

It is, therefore, in the diagnosis of the rhythms of the heart that the electrocardiographic technic finds one of its widest applications.

## STRUCTURE OF THE HEART

The next use to which the electrocardiogram may be directed is to give information about the structure of the heart.

1 From the electrocardiogram inference may be made about preponderance of one side or the other of the heart, that is to say hypertrophy. *Right axis deviation* is commonly associated with hypertrophy of the right side of the heart, such as results from the following valvular lesions: mitral stenosis (Fig 101, C), pulmonary stenosis, tricuspid disease, or from so-called pulmonary heart disease or chronic cor pulmonale: chronic asthma, bronchitis, emphysema, pulmonary fibrosis

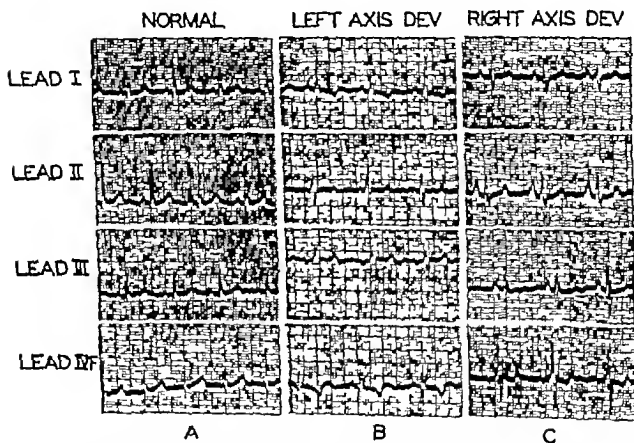


Fig 101—In A is shown a normal electrocardiogram, in B left axis deviation associated with aortic insufficiency of syphilitic etiology and in C right axis deviation associated with mitral stenosis.

and pulmonary arteriosclerosis (Ayerza's disease). In these the P waves may be increased in amplitude. *Left axis deviation* is commonly associated with hypertrophy of the left ventricle, such as occurs in aortic insufficiency (Fig 101, B), aortic stenosis, mitral insufficiency and hypertension.

In left axis deviation R-T<sub>1</sub> and perhaps R-T<sub>2</sub> may be depressed and T<sub>1</sub> negative and coved, and possibly T<sub>2</sub> negative and coved. On the other hand, in right axis deviation there may occur depression of R-T<sub>1</sub> and perhaps of R-T<sub>2</sub> together with negativity and coving of T<sub>3</sub> and perhaps of T<sub>2</sub>.

2 *Congenital malformations* of the heart may give rise to electro-



cardiographic changes to deviation of the electrical axis, or defects in QRS or P-R conduction<sup>14</sup> For instance, right axis deviation is found in pulmonary stenosis left axis deviation in coarctation of the aorta Uncomplicated patent ductus arteriosus gives rise to no deviation of the electrical axis

3 The electrocardiogram reveals data about structural damage to the heart

(a) In the first place, the electrocardiogram gives information about the conducting system from the auricles to the ventricles, in

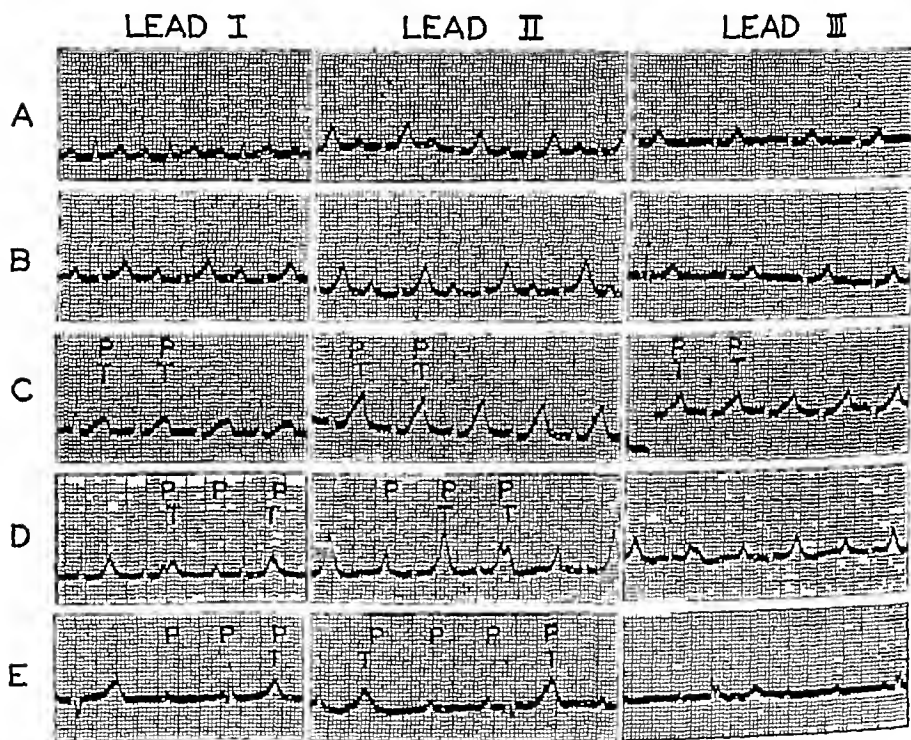


Fig 102 —A series of electrocardiograms of a patient during an attack of acute rheumatic fever with active carditis, shown in order to illustrate the range of conduction defects that may be encountered There is gradual increase in P-R conduction time in A and B and C, P and T are superimposed In D there is an occasional blocked P wave in Leads I and II, and 2:1 block in Lead III In E complete heart block prevails

that *any degree of block* may be revealed from prolonged P-R to complete heart block Alterations in the conducting system may be occasioned by (1) structural damage, such as occurs in active rheumatic infection (Fig 102), attributed also to vagal effects, in diphtheria, in gumma involving the bundle, in arteriosclerotic lesions, and in congenital defects especially when the interventricular septum is patent, (2) functional or nutritional alterations, (3) toxic effects of drugs, such as digitalis and (4) vagal effects The electrocardiogram is often

a valuable adjunct in ascertaining the activity of rheumatic infection, namely by prolongation of P-R conduction (Fig 102) and by irregularities, as well as about damage occurring in the course of diphtheria

(b) *Bundle branch block* can be diagnosed only with reliability in electrocardiograms although splitting of sounds at the apex and a bifid apex beat have been described in this lesion. The grave prognostic implications of bundle branch block are adequate reason for knowing about its presence because the duration of life is shorter in those who exhibit this defect. Bundle branch block is most commonly associated with arteriosclerotic heart disease but is occasionally a congenital

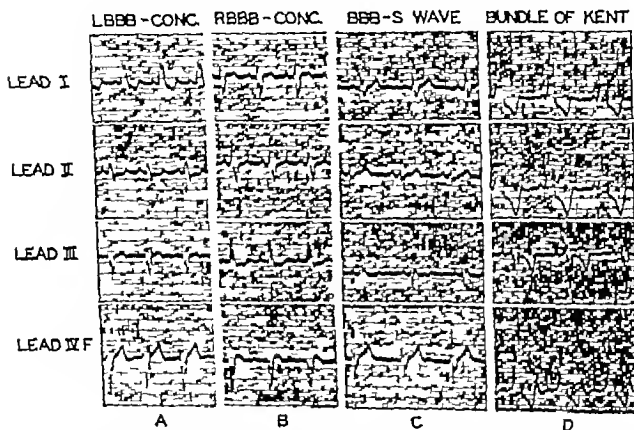


Fig 103—Electrocardiograms illustrating types of *bundle branch block* A shows left bundle branch block of concordant type, B right bundle branch block of concordant type, and C bundle branch block wide S wave type. In D is recorded an example of the so-called short P-R—long QRS, or Wolff Parkinson White or bundle of Kent syndrome.

manifestation. Electrocardiographically, bundle branch blocks can be divided into right and left varieties, each having concordant and discordant types, and the S wave type (Fig 103, A, B, C). From statistical analysis, the concordant types are associated with the shortest life span, the S wave type with the longest life span almost approaching the normal, and the discordant types with a life span intermediate between these other two.<sup>15</sup> On the other hand, bundle branch block may be transient in active rheumatic infection, or it may be functional manifestation in uremia<sup>16</sup> and in arteriosclerotic heart disease.

The so-called short P-R—long QRS (Fig 103 D), Wolff-Parkinson-

White or bundle of Kent syndrome is a congenital defect and patients exhibiting it are prone to attacks of paroxysmal tachycardia.<sup>17, 18</sup> They may have other congenital cardiac defects. The prognostic implications of this group are sufficiently different from other types of bundle branch block to warrant recognition.

(c) The situation in which the electrocardiogram yields much information is in *coronary thrombosis* or myocardial infarction. It has only been a matter of twenty-five years since Dr Herrick,<sup>19</sup> the dean of American Medicine, first described the clinical manifestations of acute coronary occlusion, and now it is a diagnosis that third-year clinical clerks can make with a reasonable degree of accuracy. It is one of the surprising events of medicine that a diagnostic entity which has been recognized scarcely twenty-five years has now come to be one of the major causes of concern and alarm for those turning 40. From the number of electrocardiographic papers dealing with the changes in this disease, one is likely to get an exaggerated sense of the value of the technic in this situation. The electrocardiogram yields, in most instances, additional evidence that acute coronary occlusion has occurred, and may give the site of location—the so-called  $T_1$  and  $T_3$  types indicating anterior apex, and posterior base locations respectively. The introduction of the chest derivations was an additional refinement in the electrocardiographic knowledge of this accident. But with the good a certain amount of evil arose due to the rapid appearance of so many chest derivations and to the difficulties inherent in standardization. The standardization of chest leads by the American Heart Association is to be commended,<sup>20</sup> for out of it comes some degree of uniformity. Several chest leads may be taken when there is indication or when the IVF derivation fails to give the expected information. Chest leads should be given a balanced place in the electrocardiographic technic.

From electrocardiograms inference can frequently be made about the extent of myocardial infarction, the part of the heart involved, conduction defects, intraventricular heart block, and about the recovery process, or more properly the evolution of changes. In this connection it is of use in therapy since it is the accepted practice to keep a patient who has suffered coronary occlusion at rest in bed until the electrocardiogram has ceased to undergo marked changes, and has become more or less stabilized, even though this period is beyond the four to eight weeks that a patient suffering acute coronary occlusion without complications is usually immobilized. In making this statement, it is realized that in some instances the electrocardiogram returns slowly to normal during a period of twelve to eighteen months. In typical cases it is now possible to distinguish certain patterns which enables the localization of the infarction, namely whether anterior apex, posterior base, or lateral. The anterior apex (anterior descending branch of left coronary artery) type is characterized early by elevation of

R-T<sub>1</sub> and maybe R-T<sub>2</sub>, depression of R-T<sub>3</sub> and elevation of R-T<sub>4</sub>, Q<sub>1</sub> and Q<sub>4</sub> may be present. In the evolution of the electrocardiogram now taken serially or day by day, there occurs a gradual transition to

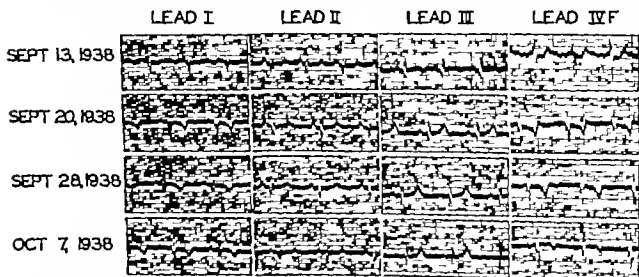


Fig 104—Serial electrocardiograms derived from a patient who had suffered myocardial infarction at the anterior apex region of the heart, illustrating the evolution of the changes, on the dates given.

negative T<sub>1</sub>, maybe negative T<sub>2</sub>, and positive T<sub>3</sub>, and negative T<sub>4</sub>, the so-called T<sub>1</sub> type of electrocardiogram (Fig 104)

The posterior base type (right coronary) is characterized by more or less opposite signs from the anterior apex type, namely early de-

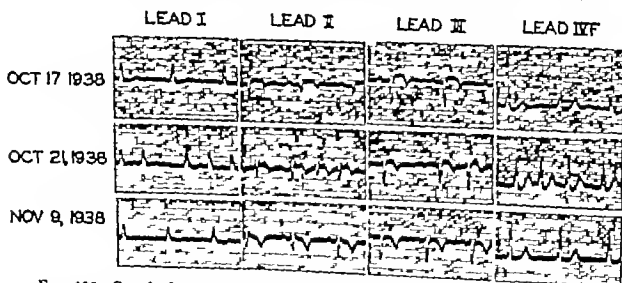


Fig 105—Serial electrocardiograms derived from a patient who had suffered myocardial infarction at the posterior base region of the heart, illustrating the evolution of the changes on the dates given. Normal rhythm was present on October 17 1938 and November 9 1938 while auricular fibrillation was present on October 21 1938

pression of R-T<sub>1</sub> and elevation of R-T<sub>2</sub> and R-T<sub>3</sub> and no change in R-T<sub>4</sub> or slight depression. As the evolution occurs there is a gradual transition to positive T<sub>1</sub> and negative T<sub>2</sub> and negative T<sub>3</sub> with up-right T<sub>4</sub> and return of R-T<sub>4</sub> to the isoelectric level if earlier it

been displaced downward. There may be a deep  $Q_3$ . This is the so-called  $T_3$  type (Fig 105). The typical form of the T waves when negative or diphasic is described as being "coved."<sup>21</sup>

In Figure 106 are shown the records of a patient who had electrocardiographic evidence of anterior apex lesion and one year later evidence of posterior base lesion. He died shortly after this last accident. At autopsy, the scar of the first myocardial infarction was seen involving the apex and the septum, (anterior apex) and the fresh infarction involving the posterior and base.

And finally, a lateral type (circumflex branch of left coronary artery) has been described, characterized by depression of R-ST in I and II and IVF.  $T_3$  is normal.<sup>22</sup> The chest lead is similar to posterior

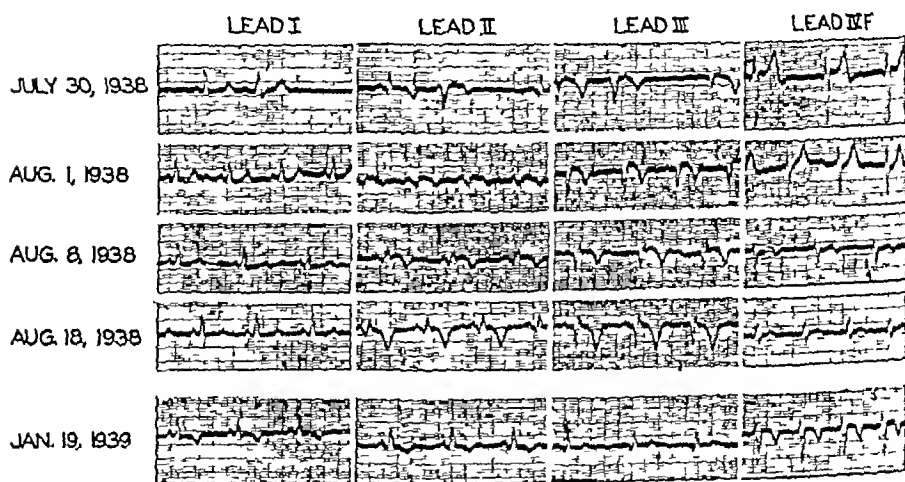


Fig 106—Electrocardiograms derived from a patient who suffered myocardial infarction first in the posterior base region of the heart, July 30, 1938 to August 18, 1938, and later, January 19, 1939, in the anterior apex region. The patient died during this last episode and autopsy revealed the old scar of the earlier posterior base infarction, and the recent infarction at the apex of the heart anteriorly.

base infarction but the three standard leads are different. There is rapid return of the electrocardiogram to normal form, so that the electrocardiographic deformity may escape record. Auricular fibrillation occurs frequently in these cases. Certain data support the definition of this electrocardiographic pattern while other studies fail to support the recognition of a typical electrocardiogram.<sup>24</sup>

Large negative  $T_4$  (15 mm) indicates that anterior apex lesion may have occurred at some time in the past and large positive  $T_4$  that a posterior base lesion may have occurred (Fig 107).

The distortion of the electrocardiogram by bundle branch block may cloud the electrocardiographic diagnosis and localization of infarction. The chance occurrence of a ventricular premature contraction may yield the typical contour to be expected.

It may be of help in prognosis to localize the infarction since it appears that the lateral ones have the least grave prognosis, the posterior base next and the anterior apex the most serious import.<sup>28</sup>

The clinical story and course pointing to acute coronary occlusion should outweigh negative electrocardiograms, even though electrocardiograms derived serially show either minor changes or none at all as occasionally is the case.

If it is possible to make them, serial electrocardiograms at few-day intervals may record changes which a single electrocardiogram may have left undetected. Serial electrocardiograms also give a record of

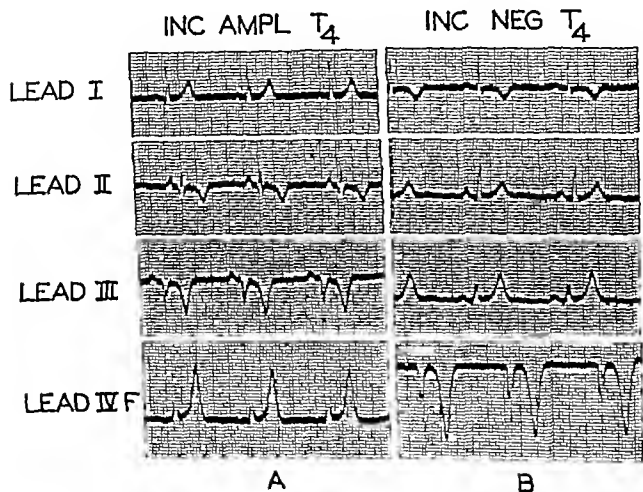


Fig 107-4 shows an instance of marked increase in amplitude of  $T_4$  and in B, an increase in negativity of  $T_4$

the evolution of changes and may be the basis for deciding upon therapy and the patient's activity

It must be kept in mind that occasionally closure of a coronary vessel may be due to coronary embolism, especially in patients suffering from subacute bacterial endocarditis. The symptoms and course and electrocardiographic patterns are, of course, similar to those resulting from coronary thrombosis.<sup>29</sup>

(d) The situation in which we would like more help from the electrocardiogram is in *coronary artery disease with coronary insufficiency*, whether the result of earlier occlusion with restoration of the

electrocardiogram to a normal configuration or the result of widespread coronary sclerosis. Certain forms of the electrocardiogram are recognized that are attributed to coronary artery changes, but it is the borderline case which lacks definiteness (see p 615)

(e) There are certain forms of the electrocardiogram with low amplitude of all complexes and splitting of the QRS waves that are attributed to myocardial disease, implying that chronic changes have occurred in the heart muscle—*fibrosis*, perhaps secondary to general decrease in blood supply, which interferes with the spread of the excitation wave through the muscle mass. They have a different contour from the large complexes and the T waves of those attributed to coronary artery disease, such as one finds in young individuals with *arteriosclerosis*, resulting from hypertension, for instance. This inference should only be made when the clinical history and age of the patient are taken into account.

(f) The electrocardiogram may undergo alterations in *trauma* such as a blow to the front of the chest, contusion, crush injury, steering wheel injury<sup>27</sup> similar to those seen in myocardial infarction with or without coronary closure. Partial heart block, sinus bradycardia, splitting of the QRS complexes, increase in amplitude of the T waves, and changes in form of the T waves going on to coving have been reported.<sup>28</sup> In stab and shotgun wounds damaging the heart, electrocardiographic changes occur. When there is ample time for operation in order to suture the heart muscle, or to ligate a severed coronary vessel, the subsequent electrocardiographic alterations correspond to those expected from the anatomical location involved,<sup>29, 30, 31, 32</sup> and resemble those seen in myocardial infarction. The changes may be modified by the presence of pericarditis.<sup>29</sup>

(g) The invasion of the heart by *primary tumors* or by *metastases* from remote or contiguous tumors may give rise to changes in the electrocardiogram.<sup>33</sup> In Boeck's sarcoid, abnormalities of the T waves may be found when the myocardium and pericardium are involved.<sup>34</sup> In leukemia there may be infiltration of the heart muscle giving rise to alteration of the T waves and conduction defects.<sup>35</sup> Xanthomatosis may be the cause of electrocardiographic changes.

(h) During *pericardial resection* in the treatment of chronic constrictive pericarditis irregularities of rhythm may occur probably in part due to mechanical stimulation of the muscle, in part to trauma to the muscle, and in part to torsion of the heart during the dissection. If auricular fibrillation prevails, ventricular premature contractions and transient ventricular paroxysmal tachycardia may occur. In the presence of normal rhythm auricular premature contractions, transient auricular fibrillation, auricular flutter and auricular paroxysmal tachycardia may be recorded.<sup>36</sup> T wave changes may continue to occur for many months afterward.

## THE ELECTROCARDIOGRAM IN DISEASE

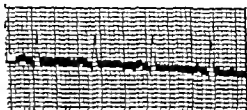
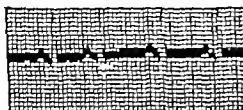
1 The electrocardiogram in *vitamin B deficiency* may show tachycardia, low voltage of the T waves, and low amplitude of QRS complexes (Fig 108) Nicotinic acid deficiency may be associated with negativity of the T waves of the electrocardiogram, the T waves become more normal after giving nicotinic acid<sup>37</sup>

2 The electrocardiogram has been found to undergo changes in *acute pericarditis*, whether due to rheumatic fever, tuberculosis, uremia, myocardial infarction, pneumonia, or to unknown etiology Many of these changes are similar to those seen in acute coronary occlusion, but an attempt has been made to make electrocardiographic distinc-

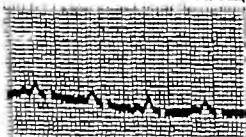
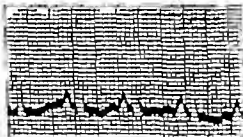
JULY 11, 1938

AUG 3, 1938

LEAD I



LEAD II



LEAD III

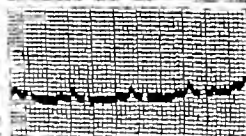
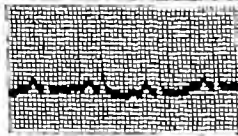


Fig 108—Two electrocardiograms of a patient who was thought to have beri beri heart disease.

tions In typical cases there is elevation of R-T segments in all three standard leads, as well as *elevation of R-T<sub>4</sub> without Q<sub>4</sub> appearing* (Fig 109) There is absence of the usual T<sub>1</sub> and T<sub>2</sub> pattern and also in the absence of the well developed Q pattern pericarditis differs from myocardial infarction. Clinically there are only few occasions in which acute pericarditis is confused with coronary occlusion even when the latter is associated with pericarditis.<sup>38</sup>

Recent papers have reported the occurrence of pericarditis with electrocardiographic changes during the course of primary atypical pneumonia and virus pneumonia.<sup>39 40</sup> The changes occurring during pericarditis<sup>41</sup>



3 The electrocardiogram in *chronic constrictive pericarditis* (Pick's disease) has been found to have surprising uniformity low amplitude of QRS and T waves throughout and perhaps coving of  $T_1$  and  $T_2$

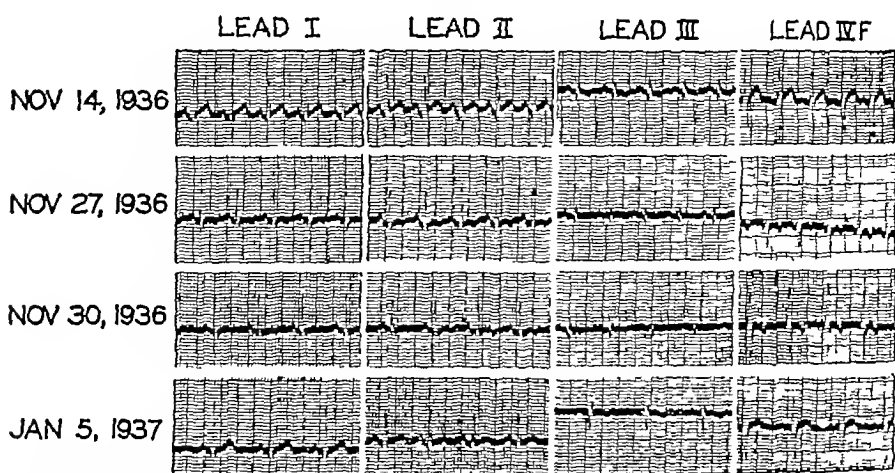


Fig 109—Serial electrocardiograms derived from a patient who had acute pericarditis of rheumatic etiology, illustrating the changes commonly observed

are common (Fig 110)<sup>42</sup> After operation, even though cure takes place, there may be surprisingly little regression of the electrocardiogram

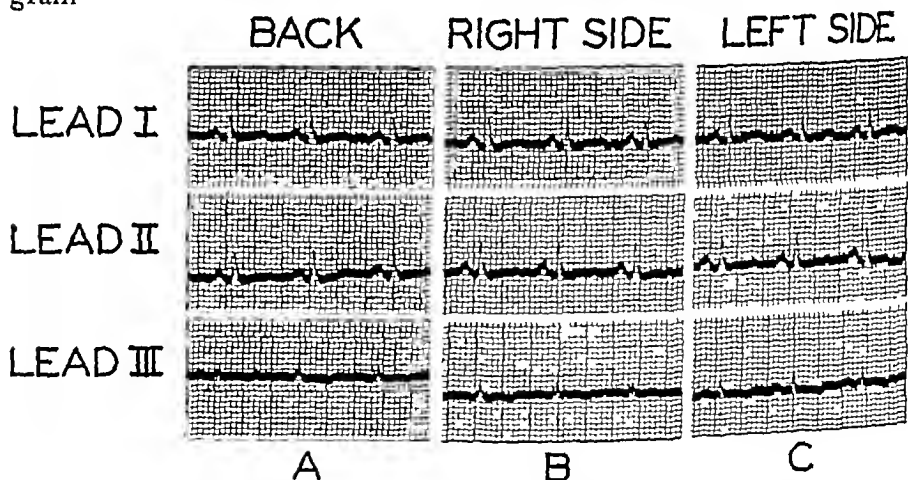


Fig 110—Electrocardiograms derived from a patient suffering from chronic constrictive pericarditis, illustrating the typical findings In A the patient was lying on his back, in B, on his right side, and in C, on his left side, in order to detect shifting of the electrical axis of the heart with change in position of the body The electrocardiogram is essentially unchanged by this procedure

4 There is another lesion which has been found to give rise to profound electrocardiographic changes which may be confused with those occurring in acute coronary occlusion, especially since its clinical

symptomatology may simulate acute coronary occlusion at times namely, *pulmonary infarction* My attention was first directed to this several years ago by the case of a woman, aged 42 years, who experienced symptoms pointing to acute coronary occlusion, pain, fall in blood pressure, rise in temperature. The electrocardiogram showed changes which were interpreted as due to acute coronary occlusion. When the patient died, a large pulmonary infarct due to a large thrombus, which had extended up from the right heart, was found at autopsy. This case made a profound impression on me and I kept on the alert for other cases—known pulmonary infarcts and electrocardiographic changes. In the meanwhile, McGinn and White<sup>43</sup> had come upon the same phenomenon and reported their cases under the title of 'acute cor pulmonale'. The electrocardiographic characteristics appear early to be staircase deformity of  $T_1$  and  $T_2$ , later low flat or

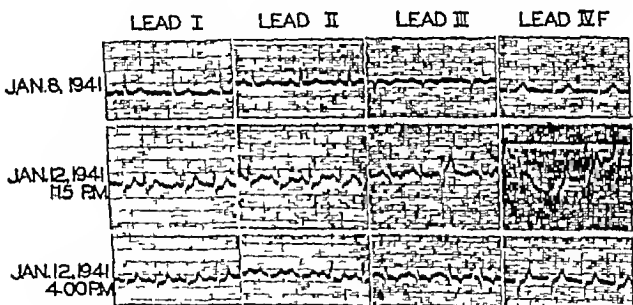


Fig 111—Electrocardiograms derived serially from a patient who had pulmonary infarction to illustrate the common changes.

inverted  $T_2$  and negative  $T_3$  and early, deep S wave in Lead I which may be split.  $T_4$  is negative and QRS complexes normal.  $T_4$  becomes upright with improvement (Fig 111).<sup>44</sup> It is similar to the  $T_3$  or posterior type of myocardial infarction. The alterations in the electrocardiograms occur in rapid succession so that the usual form of the electrocardiogram is restored earlier than in most instances of coronary occlusion. The electrocardiographic changes in pulmonary infarction are probably due to change in pressure in the pulmonary vessels. Certain experimental data dealing with this have been reported.<sup>45</sup> Overloading the circulation with fluids intravenously induces changes in the T waves and R-T segments somewhat like those in pulmonary infarction.

5 The electrocardiographic changes in *dissecting aneurysm* of the aorta or *rupture of the aorta* in *coarctation of the aorta* for example

may simulate those seen in coronary occlusion (Fig 112) This accident, however, is usually not associated with fall in blood pressure

It appears that in acute coronary occlusion, pulmonary infarction, acute pericarditis, rupture of aorta, the changes when slight may be similar and confusing, and it is likely to be just the case that the extra evidence is needed The configuration resulting from digitalis will be described later

6 Certain changes in the electrocardiograms are said to occur in *gallbladder diseases*,<sup>46</sup> and regress with removal of gallstones Since gallbladder disease occurs most commonly in the same age group as coronary artery disease, the separation of the two effects has not yet been clearly defined

7 The electrocardiogram may be turned to account in the following situation The patient has typical signs of aortic stenosis, and aortic insufficiency of rheumatic etiology There are also signs of mitral stenosis and mitral insufficiency but the question arises as to whether *mitral stenosis* is present or whether it is an *Austin Flint murmur* If there is marked aortic stenosis and aortic insufficiency, left axis deviation

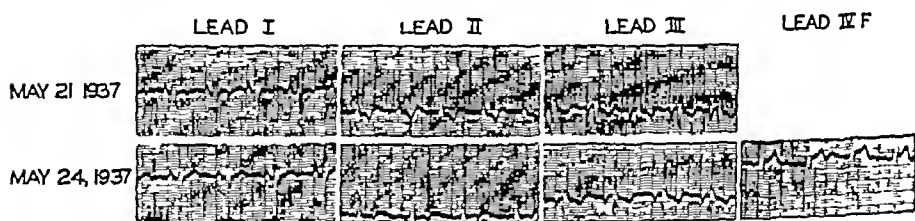


Fig 112—Serial changes in the electrocardiograms in a patient with coarctation of the aorta in whom rupture of the aorta occurred

tion is commonly present and may overbalance the right axis deviation which may have been expected in cases of mitral stenosis In cases of aortic stenosis and aortic insufficiency together with mitral stenosis, there may, however, be *no* deviation of the electrical axis (Fig 113) On the other hand, if right axis deviation had been present with the diagnosis of aortic stenosis and aortic insufficiency, that also would have been evidence of the presence of mitral stenosis

8 In a patient who is suspected of having *Fiedler's acute isolated myocarditis* the presence of bundle branch block and low amplitude of the QRS complexes may be additional evidence of the grave myocardial damage which this disease causes

9 In the course of *acute glomerulonephritis* in children<sup>47</sup> after earlier depression of R-T<sub>1 2</sub> especially, there may be flattening or inversion of T waves in one or more leads, in T<sub>3</sub> as often as in T<sub>1</sub> Heart failure was more common in those with T<sub>1</sub> inversion

10 Most patients with *cardiovascular syphilis* have abnormal electrocardiograms Left axis deviation occurs when aortic insufficiency is present. There may be anterior apex pattern of the electrocardiogram

due to involvement of the coronary ostia Auriculoventricular as well as bundle branch block have been recorded<sup>43</sup>

11 Electrocardiographic changes have been described in *Friedreich's disease* conduction defects including complete heart block with Stokes-Adams syndrome are common Bundle branch block and T wave abnormalities have also been described<sup>40</sup>

12 In *trichinosis* there may be clinical and electrocardiographic evidence of myocardial involvement The cardiac manifestations are said to be due to active migration of the larvae to the myocardium and not to a toxic substance. The electrocardiographic changes are in the T

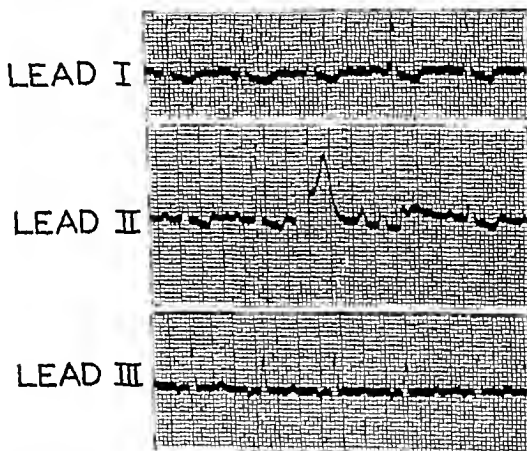


Fig 113—Electrocardiogram from a patient who had mitral stenosis and in sufficiency and aortic insufficiency illustrating the absence of deviation of the electrical axis.

waves with the development of negativity of  $T_2$  and  $T_3$  and alteration of  $T_4$ <sup>50 51</sup> From the nature of the myocardial lesions a characteristic electrocardiogram is hardly to be expected

13 Transient alterations of the T waves of the electrocardiogram have been reported in *acute pancreatitis*<sup>52</sup> Depression of the R-T segments which might be confused with infarction of the lateral wall of the left ventricle have been described in *perforation of a gastric ulcer*<sup>53</sup>

14 Transient changes have been recorded in the T waves of the electrocardiogram as well as prolongation of the P-R time during the course of *epidemic parotitis*<sup>54</sup>

15 Electrocardiographic alterations have been recorded during *epileptic seizures*, and T waves may decrease in amplitude<sup>55</sup> or increase in amplitude. Metrazol convulsions result in increase in amplitude of the T waves and many types of irregularities of the heart rhythm, namely both auricular and ventricular premature contractions, nodal rhythm, increase in P-R conduction, going on to incomplete and complete heart block<sup>56</sup>. Electrical convulsions may give rise to essentially similar changes, namely increase in amplitude of the T waves, both auricular and ventricular premature contractions, and nodal rhythm<sup>57</sup>.

16 Nonspecific transient changes in the T waves have been described in *scarlet fever* but rarely conduction defects<sup>58</sup> <sup>59</sup>. Transient alterations of the T waves may be recorded in *acute tonsillitis*.

17 Changes in the T waves may be observed in any of the acute infections such as *acute osteomyelitis with bacteremia*. Changes in rhythm and T waves have been described in *spirochetal jaundice*<sup>60</sup>.

18 The following alterations have been recorded during and following *diabetic coma*<sup>61</sup>: lengthening of the Q-T interval, depression of the R-T interval and inversion of the T waves. The most marked changes occurred not during coma but twenty-four hours later when the patients had improved.

19 In *chronic and severe anemia* T waves may be flattened, and less frequently, depression of R-T segments and low voltage of the QRS complexes<sup>62</sup>. On the other hand, there may be no marked alterations in pernicious anemia<sup>63</sup>.

#### ELECTROCARDIOGRAM AND POSITION OF THE HEART

The electrocardiogram can be used to give information about the position of the heart, and conversely, the position of the heart has to be taken into account in reading the electrocardiograms.

1 The *body build* of the subject alters the electrocardiograms. Short, stout subjects tend to induce left axis deviation, and the long, narrow type to give rise to right axis deviation.

2 The form of the electrocardiogram in *dextrocardia* may be placed under this rubric, the physical examination of the subject should reveal this deviation from the usual and confirmation secured by fluoroscopy and x-ray examination (Fig 114, A). In the electrocardiogram Lead I appears to be upside down, and Leads II and III to be interchanged (Fig 114, B).

3 *Pneumothorax, collapse of lung, large pleural effusion* and *chest deformity* alter the electrocardiogram by shifting the heart. *Pregnancy* and *ascites* by raising the diaphragm tend to give left axis deviation. In pregnancy Q<sub>3</sub> may develop together with a negative T wave in Lead III<sup>64</sup>.

4 *Interstitial emphysema* which may be confused clinically with *acute coronary occlusion*<sup>65</sup>. In them electrocardiographic changes do

not occur. Interstitial emphysema occurs usually in younger individuals than does coronary occlusion.

5 In *chronic constrictive pericarditis*, the fixation of the heart in the electrocardiogram<sup>45</sup> combined with fixation of the point of maximal impulse clinically and fluoroscopically is additional evidence in

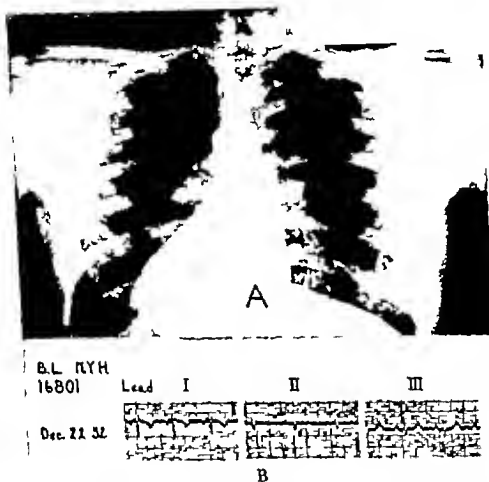


Fig 114—A A 2 meter x ray photograph of the chest showing the position of the heart B, the electrocardiogram derived from this patient with dextrocardia.

summing up the evidence for Pick's disease. It is recalled that large hearts may not shift, but the constricted hearts are usually not much enlarged thereby giving more weight to this sign. The fixation of the electrical axis, even though the position of the body is changed is shown in Figure 110

#### PHARMACOLOGICAL AND THERAPEUTIC USES

So much for information about structure. To what pharmacologic uses and the management of what drugs in the course of therapy may the electrocardiogram be directed?

1 It is fitting that *digitalis* should be mentioned first. Cohn and Jamieson<sup>60</sup> first studied the changes induced in the electrocardiogram by *digitalis*. This has been frequently confirmed.<sup>61</sup> The changes occur in the T waves and R-T segments in any of the three leads the T waves may become lower in amplitude, or go on to negativity, or if

negative they may become upright (Figs 115 and 116) Prolonged P-R conduction and heart block may occur if toxic amounts have been given

(a) Changes in the T waves and R-T segments are not an indication of the degree of digitalization for they may occur with amounts

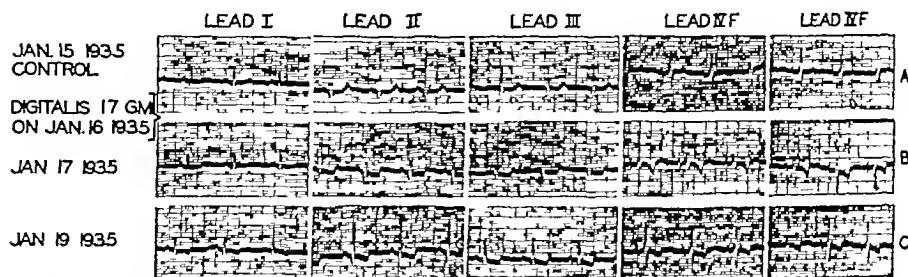


Fig 115—Electrocardiograms showing the effects of digitalis on the four leads of the electrocardiogram when there is regular sinus rhythm showing alterations in T waves, R-T segments, and heart rate. Electrocardiogram A was taken before, B, twenty-four hours after 17 gm of digitalis by mouth in twenty-four hours, and C, two days later. In the chest leads in the first column designated IVF the chest electrode was placed at the apex and in those in the second column designated IVF it was placed about 1 cm beyond the apex. In this instance there was no marked difference (Stewart, H J and Watson, R F. *Am Heart J*, Vol 15)

short of therapeutic ones.<sup>68</sup> Digitalis given by mouth may give electrocardiographic changes in one to two hours, and in slightly shorter time when given by rectum, and in shorter time still when given intravenously.

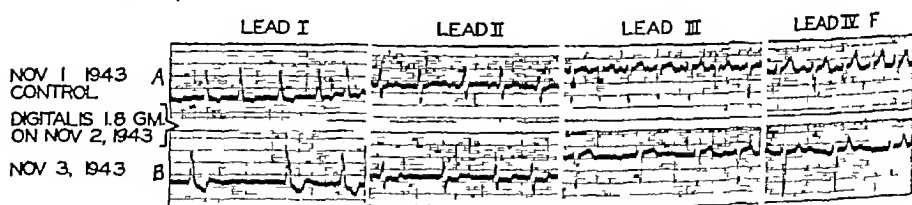


Fig 116—Electrocardiograms showing the effect of digitalis on the four leads of the electrocardiogram when there is auricular fibrillation. A served as a control. The patient was given 1.8 gm digitalis by mouth on November 2, 1943. B, taken on November 3, 1943, shows increased negativity and change in form of the T waves in Leads I and II, with change in form of the T waves in Leads III and IVF.

(b) In patients with normal sinus rhythm—when digitalis is used, an occasional electrocardiogram may prevent overdigitalization if changes in P-R time are detected. Therapeutic amounts of digitalis do not usually cause conduction defects (Fig 115).

(c) Ventricular premature contractions clinically and in the electrocardiogram may indicate overdigitalization.

(d) The electrocardiographic changes in the chest lead occurring with digitalis may simulate those attributed to coronary occlusion and for this reason the question of the use of digitalis must be taken into account in reading electrocardiograms (Figs 115 and 116).<sup>67</sup>

(e) With great rarity transient bundle branch block has been observed following overdigitalization.

(f) Calcium and digitalis have somewhat similar effects on heart muscle and should not be given simultaneously.<sup>68</sup> Ventricular premature contractions appear with smaller amounts of digitalis when calcium is given intravenously,<sup>70</sup> and deaths have been reported following the use of calcium salts intravenously in digitalized patients.<sup>71</sup> The results of experiments in animals with normal heart muscle may not be applicable to instances of heart disease in the clinic.<sup>72</sup>

2 In long-continued use of *quinidine* in the treatment of ventricular premature contractions and recurrent ventricular paroxysmal

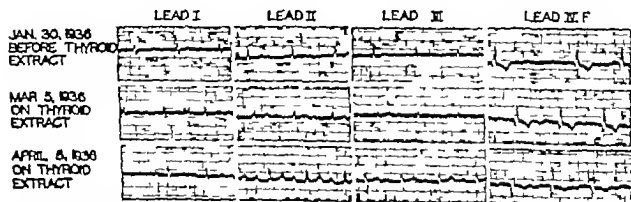


Fig 117—Series of electrocardiograms derived from a patient suffering from spontaneous myxedema, illustrating the low amplitude of the QRS complexes, and the conduction defect followed by repression of changes when the patient was given thyroid extract. (Stewart H J, Dietrich J E and Crane, N F J Clin. Investigation, Vol. 17)

tachycardia, as well as in the use of larger amounts to terminate abnormal rhythms, the prolongation of the QRS time may be an early toxic sign. Recent studies<sup>73</sup> have shown that *atabrine* and *quinine* decrease the amplitude of the T waves and *plasmaquin* increases the amplitude of the T waves above normal.

3 In a typical case of myxedema the R and T waves are of low voltage and the P-R time prolonged (Fig 115, Jan 30, 1936). With the administration of *thyroid extract* the P-R time decreases and the amplitude of the T waves and R waves increases (Figs 117, March 5 and April 8, 1936). The reaction is a reversible one.<sup>74</sup> It is important to watch therapy carefully if patients are in the coronary age group because coronary occlusion may occur while under therapy. On the other hand the electrocardiographic picture in *hyperthyroidism* is not diagnostic or characteristic at times the T waves being tall and pointed and at other times tall and rounded.<sup>75</sup>



4 *Nicotine* will be mentioned briefly. There is no uniformity of opinion about the effect of tobacco on the heart.<sup>70</sup> Nevertheless, in certain patients smoking may be associated with pain, palpitation, or

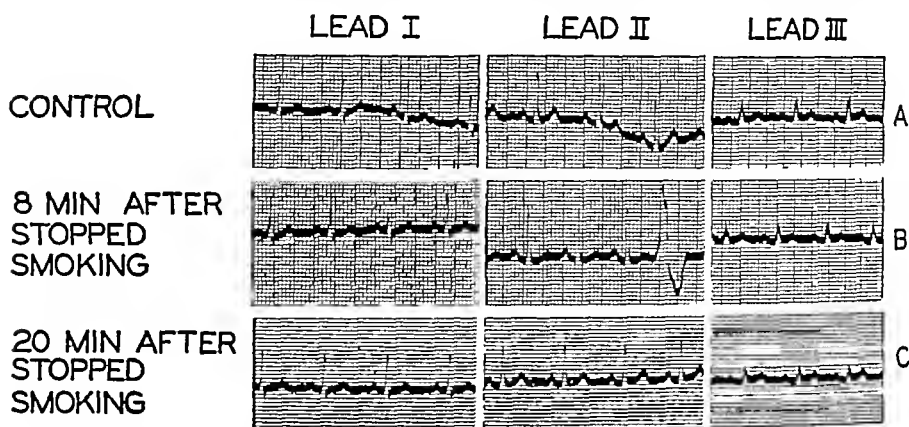


Fig 118—Effects of smoking cigarettes in a patient who experienced irregularity of the heart and precordial distress on smoking. After the control (A) was taken the patient smoked for ten minutes. Frequent electrocardiograms were taken. B was taken eight minutes, and C twenty minutes after he stopped smoking. The time marker was not running while C was taken.

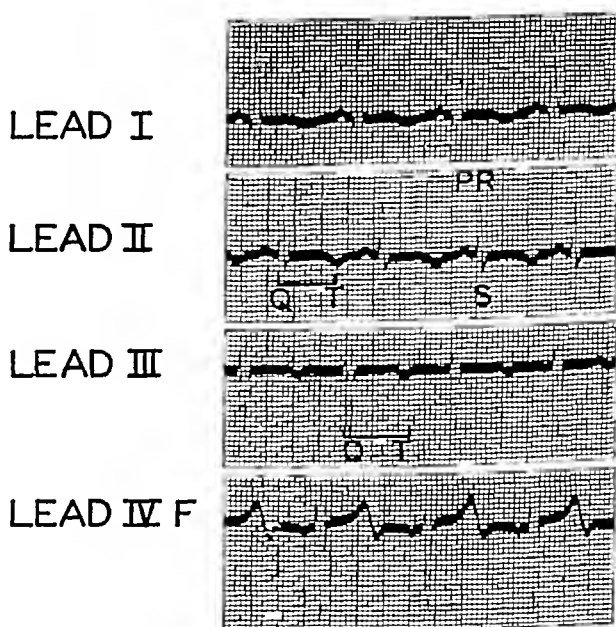


Fig 119—An electrocardiogram showing prolongation of the Q-T interval associated with chronic nephritis with uremia.

irregularity of the heart. Records are reproduced of a patient, aged 20 years, in whom smoking gave rise to changes in the form of the T waves and R-T segments, especially T<sub>2</sub>, tachycardia, ventricular pre-

mature contractions (Fig 118) and to precordial distress. The most consistent effect on the electrocardiogram after smoking has been found to be decrease in amplitude of the T waves.<sup>77 78</sup>

5 At times, *hypocalcemia* may be hypothecated from the electrocardiogram when the Q-T interval is prolonged<sup>79</sup> when it has not been suspected clinically (Fig 119). The Q-T prolongation may occur in patients with chronic gastrointestinal lesions, chronic nephritis, or hypoparathyroidism.

6 The use of *potassium salts* may give marked changes in the electrocardiogram and lead to abnormalities of conduction, abnormal rhythms and cardiac standstill by depression of the activity of the sinus node (Fig 120).<sup>80 81 82</sup>

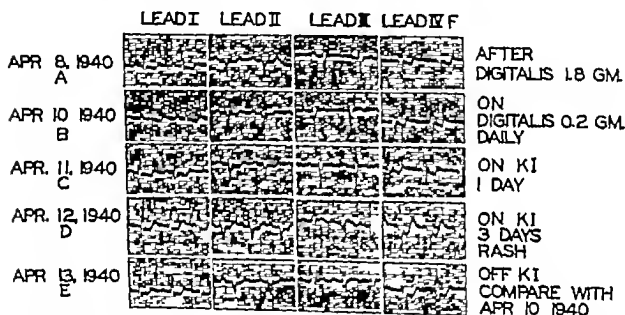


Fig 120—A series of electrocardiograms derived from a patient who was given potassium iodide. A was taken after digitalization and B while the patient was on maintenance amounts of digitalis, during which time the electrocardiogram remained constant; these two records served as controls. C and D show the changes induced by potassium iodide and E shows reversion of the electrocardiogram to its control forms, A and B, after potassium iodide was discontinued (Stewart, H. J. and Smith, J. J. *Am J M. Sc.*, Vol 201)

7 On the other hand abnormalities of the electrocardiogram—QRS conduction and T waves—have been recorded in familial periodic paralysis, which are reversed by the administration of potassium salts (Fig 121).<sup>83</sup>

8 *Acute blood loss* may lower the T waves, even to their becoming isoelectric or negative. Depression of the R-T segments and lowering of the amplitude of the QRS complexes may result. The changes persist for two to nine days.<sup>84 85</sup> The alterations may be due to lesions in the myocardium caused by insufficient blood supply.

9 Sympathetic stimulation occasioned by *exercise* or *fear* or *adrenaline*<sup>86</sup> and vagal inhibition resulting from *atropine* lowers the T waves in Lead II even to the point of inversion. On the other hand, vagal

stimulation caused by *ergotamine tartrate* and after exercise raises the T waves

10 In patients suffering from angina who have abnormal electrocardiograms, *nitroglycerin* restores the electrocardiogram to a more normal form<sup>87</sup> (see p 615)

11 *Nicotinic acid* in large amounts (300 mg) which induces flushing has been found to prevent the occurrence of angina pectoris resulting from exercise and also to restore the deformity of the T waves and R-T segments of the electrocardiogram caused by exercise to a more normal contour, presumably by dilatation of the coronary vessels sharing in the generalized vasodilatation<sup>88</sup> (see anoxemia test, p 616)

12 Mention (p 593) has already been made of the use of *mecholy* in the treatment of supraventricular paroxysmal tachycardia Mecholy!

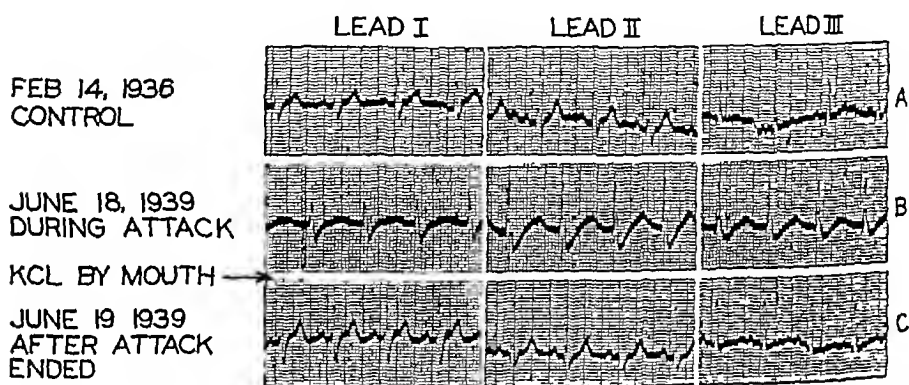


Fig 121—Changes apparent in the electrocardiogram in *familial periodic paralysis* A, taken when the patient was feeling well, serves as a control B was taken during an attack of paralysis, following which 42 gm of potassium chloride was given by mouth C was taken after the attack had terminated as the consequence of giving potassium chloride Serial electrocardiograms which were taken after ingestion of potassium chloride showed the gradual regression of the electrocardiograms' defects (Stewart, H J., Smith, J J and Milhorat, A T Am. J Med Sc., Vol 199)

may induce any grade of heart block, from prolongation of the conduction time to incomplete heart block and complete heart block<sup>89</sup> through its parasympathetic effects Atropine abolishes these effects

13 During *surgical anesthesia* variations in amplitude of the QRS complexes and T waves, shifting of the R-T segment and changes in P-R interval occur frequently Arrhythmias are more common in abnormal hearts than in normal ones Premature contractions, complete heart block, paroxysmal auricular fibrillation and irregularity of the ventricles have been recorded Changes may persist for many hours following anesthesia The highest incidence of irregularities occurred in chloroform anesthesia There is apparently no correlation between the occurrence of abnormalities and the depth of anesthesia or the surgical procedure<sup>90</sup>

## USE OF ELECTROCARDIOGRAM IN FUNCTIONAL TESTS

And finally, can the electrocardiogram be used to give information about function? Sporadic attempts have been made to turn this technic to account in estimating the functional capacity of the heart but it has remained for Levy to pursue it systematically.

Many patients in whom the differential diagnosis of angina pectoris arises present electrocardiograms which are essentially normal and it was to the elucidation of the objective diagnosis of coronary insufficiency that Levy directed the use of electrocardiograms.

1 It has long been known that the electrocardiogram may undergo changes in the T waves and R-T segments during an attack of angina pectoris only to assume its usual form with the passing of the attack. When changes occur it is useful in the differential diagnosis of angina

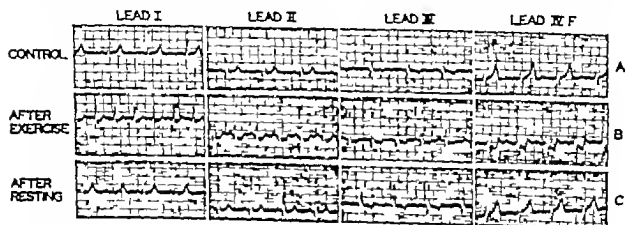


Fig 122—Electrocardiograms illustrating the effects of exercise in a patient suffering from angina pectoris. After resting one-half hour the control electrocardiogram (A) was taken B was taken after the patient had walked over three steps for fifty times with the induction of precordial pain and shows depression of the R-T segments in Leads I, II and IV F C was taken after resting and shows restoration of the electrocardiogram to its control form.

2 In patients who experience precordial distress, it is important to decide whether the pain is associated with cardiac disease and whether it is angina pectoris. Since typical angina is associated with effort, the effect of exercise on electrocardiograms has been studied together with a correlation of the occurrence of pain. By inference appropriate electrocardiographic changes are interpreted as evidence of impairment of the coronary circulation. In certain patients with coronary artery disease marked alterations of the T waves and R-T segments occur during exercise, going on to negativity and depression of these components respectively changes which disappear shortly after resting (Fig 122).

In spontaneous angina and that resulting from the exercise test, the electrocardiographic changes are attributed to transient alterations in the myocardium because of inadequacy of the coronary circulation in short to anoxemia of the heart muscle or to the accumulation of metabolites.

3 Levy has studied patients exhibiting angina pectoris during the anoxemia induced by breathing a mixture of 10 per cent oxygen and 90 per cent nitrogen and found that in certain ones pain occurred and in others it did not. In short, pain being subjective was not a dependable sign, as a consequence he sought for objective data which the use of electrocardiograms supplied. He devised an *anoxemia test* using electrocardiographic changes as the objective record.<sup>91</sup> He has defined the changes in the T waves and R-T segments of the three standard leads and chest lead that may be expected in normal individuals when subjected to the test and contrasted them with those occurring in patients exhibiting coronary artery disease.

The test is said to be "positive when anyone of the following is found (1) the arithmetic sum of the R-ST deviations in all four leads (I, II, III and IVF) totals 3 mm or more (2) There is partial or com

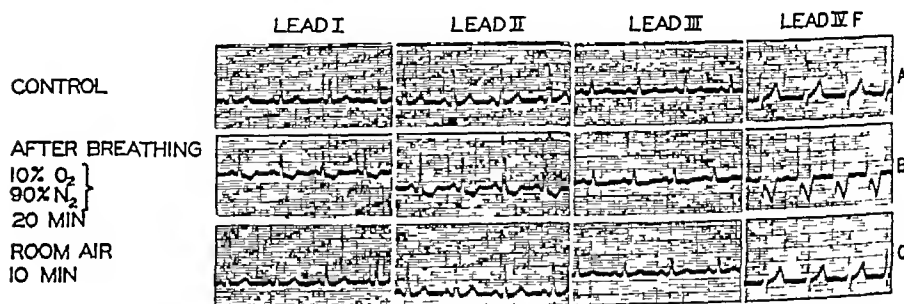


Fig 123—Electrocardiograms in an anoxemia test exhibiting "positive" changes in a patient suffering from angina pectoris. *A* was the control record. *B* was taken after breathing 10 per cent oxygen and 90 per cent nitrogen for twenty minutes. *C* was taken twenty minutes after breathing room air. Attention is directed to occurrence of negativity of the T waves in Leads I, II, III and IVF, while breathing the low oxygen, and reversion to the control form after breathing room air.

plete reversal of the direction of the T waves in Lead I, accompanied by an R-ST deviation of 1 mm, or more, in this lead (3) There is complete reversal of the direction of the T wave in Lead IVF, regardless of any associated R-ST deviation in this lead."<sup>91</sup>

This test gives promise of giving valuable additional information when the symptoms are not typical or not clearly defined and may be helpful in separating malingerers from those suffering true angina pectoris.

The exercise test is positive at times when the anoxemia test is negative, and at other times is negative when the anoxemia test is positive or both may give positive tests.<sup>92</sup>

In Figure 123 are reproduced the electrocardiograms in a so-called positive anoxemia test in which breathing the 10 per cent oxygen 90 per cent nitrogen mixture was associated with marked negativity of

T<sub>1</sub> 2 3 4 with depression of R-T<sub>1</sub> 2 3 4 and also subjectively with pain, both of which were promptly dissipated by breathing room air for ten minutes

4 Occasionally the symptoms associated with hiatus hernia may be confused with those of angina<sup>83 84</sup> In *hiatus hernia* electrocardiographic changes do not occur unless the patient also has coronary artery disease. The anoxemia test may be used in the differential diagnosis of these two entities

5 Occasionally *pulsus alternans* which is evidence of grave myocardial weakness is associated also with electrical alternans in the electrocardiogram (Fig 124)

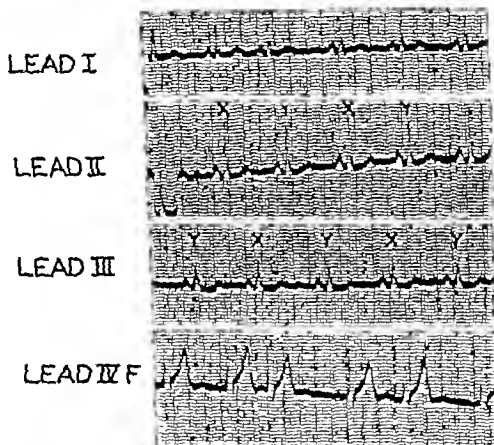


Fig 124—Electrocardiograms illustrating electrical alternans in a patient suffering from severe myocardial disease due to arteriosclerosis. "X" indicates the taller QRS complexes and "Y" the lower ones.

#### FUNCTIONAL DISEASES

The electrocardiogram has been more useful in its contributions to organic heart disease than in so-called functional heart disease, except by its negative evidence. For instance, in *neurocirculatory asthemia* there may be transient changes in the T waves. T<sub>2</sub> may be flattened or even inverted<sup>85</sup> probably due to preponderant sympathetic nerve imbalance. T<sub>2</sub> may become upright with improvement.

Marked electrocardiographic changes may be induced by fear. When there is increase in amplitude of the P and T waves, it has been attributed to sympathetic stimulus of the contractions of the heart.

There may be more marked changes amplitude of the QRS complexes may decrease, T wave deflections may become negative, and R-T segments descend below the the isoelectric level and become deformed, changes which have been attributed to coronary constriction caused by vagal stimulation<sup>96</sup>

There may be disturbing symptoms brought about by *hyperventilation*<sup>97 98</sup> There may be flattening of the T waves with hysterical overventilation and tetany, just as *alkalosis* from voluntary overventilation or from ingestion of sodium bicarbonate reduces the amplitude of T waves On the other hand, *acidosis* produced by exercise or ingestion of ammonium chloride increases the amplitude of T waves<sup>99</sup>

### CONCLUSIONS

The general pattern of an individual's electrocardiogram with continued good health remains remarkably constant over long periods of time It appears, however, that here is a large variety of diseases, drugs, emotional states, and events (eating, drinking) in the course of the business of living which induce transient, prolonged or permanent impressions on an individual's electrocardiographic pattern The most common of these have been mentioned in order to convey an impression of wide range of the factors which have to be taken into consideration in the interpretation of electrocardiograms It should be emphasized that the clinical history and findings should be utilized in arriving at the correct interpretation for it is only in a few instances that the patterns are sufficiently characteristic to be related to their proper origin Among these few are the irregularities, typical coronary occlusion patterns, typical pulmonary infarction patterns, typical pericarditis patterns, and typical digitalis effects Moreover, instances have been related to illustrate how disease remote from the heart may alter the electrocardiogram by indirection the shock of acute peritonitis from perforation of gastric ulcer, the disturbed components of the blood and change in blood pressure in diabetic coma, etc , may be cited as examples

A word on the misuse of electrocardiograms may be in order They are now and then requested with this inquiry "Can the patient be operated upon?" It is apparent that electrocardiograms do not yield this kind of information about function A careful physical examination and history are much more important to answer that question In the formulation of the case, an electrocardiogram may contribute and yield certain information that plays its part in the intelligent evaluation of the case, but as an isolated observation it cannot make such a decision

The electrocardiogram therefore may be used to contribute information about rhythm, structure, position of heart, data which contributes to the whole clinical picture, therapy, effect of drugs, emotions, and function The electrocardiogram has made enormous contributions to

our knowledge of heart disease, and the technic can be used to contribute to the skilled diagnosis and treatment of patients, but an electrocardiogram is not necessary in the case of every patient that the physician sees or of every patient with heart disease in order to make a correct diagnosis or to carry out careful, correct treatment. If one is fully aware of its limitations there is no reason, however, for not taking electrocardiograms in any cases one wishes or making the work-up as complete as possible or using them for gaining further information, in short, as an investigative weapon. The implement is being made more and more available both as a consequence of improvement and simplification of machinery, and by the education and heart consciousness of the public, but in order to meet both forces it is necessary that the electrocardiograms be interpreted (1) by those who have had ample training (2) and by those who are interested not only in heart disease but also general medicine for the sake of a balanced and not too one-sided viewpoint and (3) finally it is necessary that an intelligent use of electrocardiograms and recognition of the situations in which help may be expected from this technic should be kept in mind.

## BIBLIOGRAPHY

- 1 Stewart, H. J. and Bailey, R. L. The Effect of Posture on the Form of Pre-cordial Leads of the Electrocardiogram. *Am Heart J.*, 18:271 1939
- 2 White, P. D., Chamberlain, F. L. and Graybiel, A. Inversion of the T Waves in Lead II Caused by a Variation in Position of the Heart. *Brit. Heart J.*, 3:233 1941
- 3 Wilson, F. N. and Finch, R. The Effect of Drinking Iced Water Upon the Form of the T Deflection of the Electrocardiogram. *Heart*, 10:275 1923
- 4 Gardberg, M. and Olsen, J. Electrocardiographic Changes Induced by the Taking of Food. *Am Heart J.*, 17:725 1939
- 5 Graybiel, A., McFarland, R. A., Gates, D. C. and Webster, F. A. Analysis of the Electrocardiograms Obtained from 1,000 Young Healthy Aviators. *Am. Heart J.*, 27:524 1944
- 6 Mackenzie, J. Digitalis. *Heart*, 2:273 1911
- 7 Stewart, H. J.. Functional Disorders of the Heart. *Cardiac Arrhythmias. Cecil's Textbook of Medicine*, 6th ed Philadelphia, W. B. Saunders Co., 1943 p. 1111
- 8 Stewart, H. J. The Use of Digitalis in the Treatment of Auricular Premature Contractions. *Am. Heart J.*, 1:687 1926
- 9 Ray, B. S. and Stewart, H. J. Observations and Surgical Aspects of the Carotid Sinus Reflex in Man. *Surgery* 11:915 1939
- 10 Stewart, H. J., Dietrick, J. E., Crane, N. F. and Thompson, W. P. Studies of the Circulation in the Presence of Abnormal Cardiac Rhythms. Observations Relation to (Part I) Rhythms Associated with Rapid Ventricular Rate and to (Part II) Rhythms Associated with Slow Ventricular Rate. *J. Clin. Investigation* 17:449 1938 (also bibliography)
- 11 Currie, G. M. Transient Inverted T Waves After Paroxysmal Tachycardia. *Brit. Heart J.*, 4:149 1942
- 12 Gelger, A. J. Electrocardiograms Simulating Those of Coronary Thrombosis After Cessation of Paroxysmal Tachycardia. *Am. Heart J.*, 26:555 1943
- 13 Campbell, M. Inversion of T Waves After Long Paroxysms of Tachycardia. *Brit. Heart J.*, 4:49 1942.



- 14 Schnitker, M A The Electrocardiogram in Congenital Cardiac Disease, 1st ed Cambridge, Mass, Harvard University Press, 1940
- 15 Willius, F A, Dry, T J and Reeser, R., Jr Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram I General Considerations of Bundle Branch Block with Concordant and with Discordant Graphs and the Wide S Wave Pattern, Based on 1611 Cases Arch Int Med, 67 1008, 1941
- 16 Moore, N S and Stewart, H J The Disappearance of Intraventricular Heart-Block Occurring in Uremia Following the Intravenous Injection of Hypertonic Glucose Solutions Am Heart J, 5 469, 1930
- 17 Wolff, L, Parkinson, J and White, P D Bundle Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia. Am Heart J., 5 685, 1930
- 18 Wood, F C, Wolferth, C C and Geckler, G D Histologic Demonstration of Accessory Muscular Connections between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex Am Heart J., 25 454, 1943
- 19 Herrick, J B Clinical Features of Sudden Obstructions of the Obstruction of the Coronary Arteries J.A.M.A., 59 2015, 1912
- 20 Standardization of Precordial Lead Joint Recommendation of the American Heart Association and the Cardiac Society of Great Britain and Ireland. Am Heart J, 15 107, 235, 1938
- 21 Pardee, H E. B An Electrocardiographic Sign of Coronary Artery Obstruction Arch Int Med., 26 244, 1920
- 22 Wood, F C., Wolferth, C C and Bellet, S Infarction of the Lateral Wall of the Left Ventricle Electrocardiographic Characteristics Am Heart J, 16 387, 1938
- 23 Thomson, H W and Feil, H Infarction of the Lateral Wall of the Left Ventricle, Pathologic and Electrocardiographic Study Am J Med Sc., 207 588, 1944
- 24 Shaffer, C F Electrocardiographic Study of Lateral Infarction, Proved at Autopsy Am Heart J, 28 39, 1944
- 25 Baer, S and Frankel, H Studies in Acute Myocardial Infarction III Diagnosis and Location of the Infarct by Electrocardiogram Arch Int Med., 73 286, 1944
- 26 Hamman, L Coronary Embolism Am Heart J, 21 401, 1941
- 27 Arenberg, H Traumatic Heart Disease A Clinical Study of 250 Cases of Non-Penetrating Chest Injuries and Their Relation to Cardiac Disability Ann Int Med 19.326, 1943
- 28 Barber, H Electrocardiographic Changes Due to Trauma. Brit. Heart J., 4 83, 1942
- 29 Fraser, W A and Myer, T Electrocardiographic Findings Associated with a Gunshot Wound of the Heart New England J Med., 225 286, 1941
- 30 Olm, C B and Hughes, J D Stab Wound of the Heart with Coronary Ligation J Thoracic Surg., 9-99, 1939
- 31 Elkin, D C and Phillips, H S Stab Wound of the Heart. Electrocardiographic Studies of Two Cases J Thoracic Surg, 1 113, 1931
- 32 Solovay, J, Rice, G D and Solovay, H U Electrocardiographic Changes in Stab and Gunshot Wounds of the Heart, with Review of the Literature Ann Int Med., 15 465, 1941
- 33 Rosenbaum, F F, Johnson, F D and Alzamora, V V Persistent Displacement of the RS-T Segment in a Case of Metastatic Tumor of the Heart. Am Heart J., 27-667, 1944
- 34 Longcope, W T and Fisher, A W Involvement of the Heart in Sarcoidosis or Besnier-Boeck-Schaumann's Disease J Mt Sinai Hosp, 8 784, 1942

- 35 Blotner H. and Sosman, M. C. X-ray Therapy of the Heart in a Patient with Leukemia, Heart Block and Hypertension. *New England J Med.*, 230 793, 1944
- 36 Stewart, H J and Bailey R L. Changes in the Rhythm of the Heart During Resection of the Pericardium in Chronic Constrictive Pericarditis, as Recorded Electrocardiographically. *Am. Heart J.*, 22 169 1941
- 37 Rachmulewitz, M and Braun, K. The Presence of Electrocardiographic Changes in Nicotinic Acid Deficiency and Their Elimination by Nicotinic Acid. *Am Heart J.*, 27 203, 1944
- 38 Bellet, S and McMillan, T M. Electrocardiographic Patterns in Acute Pericarditis. Evolution Causes, and Diagnostic Significance of Patterns in Limb and Chest Leads. Study of Fifty-Seven Cases. *Arch Int. Med.*, 61 381 1938
- 39 Wolff L. Acute Pericarditis Simulating Myocardial Infarction. *New England J Med.*, 250 442 1944
- 40 Findelstein, D and Klainer M J. Pericarditis Associated with Primary Atypical Pneumonia. *Am Heart J.*, 28 385 1944
- 41 Master A. M., Romanoff A. and Jaffe, H. Electrocardiographic Changes in Pneumonia. *Am Heart J.*, 6 696, 1931
- 42 Stewart, H J and Heuer G J. Chronic Constrictive Pericarditis. Dynamics of the Circulation and Results of Surgical Treatment. *Arch Int. Med.*, 63 504 1939
- 43 McGinn, S. and White, P D.. Acute Cor Pulmonale Resulting from Pulmonary Embolism Its Clinical Recognition. *J.A.M.A.*, 104 1473 1935
- 44 Stewart, H J., Kirk, R. C. and Smith, J J. Electrocardiographic Changes in Pulmonary Infarction. *New International Clinics 3 Series*, 3 135, 1940.
- 45 Love, W S., Jr., Brugler G W and Winslow, N. Electrocardiographic Studies in Clinical and Experimental Pulmonary Embolization. *Ann Int. Med.* 11 2109 1938
- 46 Fitz Hugh T and Wolferth, C. C. Cardiac Improvement Following Gall Bladder Surgery. *Ann Surg.*, 101 478 1935
- 47 Ash R., Rubin, M I. and Rapoport, M. Electrocardiographic Variations in Acute Glomerulonephritis. *Am. J Dis. Child.*, 67 106, 1944
- 48 Cole, S L and Bohning A. Electrocardiographic Patterns in Cardiovascular Syphilis. *Am. J M Sc.*, 207 317 1944
- 49 Evans, W and Wright G. Electrocardiograms in Friedreich Disease. *Brit. Heart J.*, 4 91 1942.
- 50 Cushing E. H. Electrocardiographic Changes in Trichinosis. *Am Heart J.*, 11 494 1936
- 51 Beecher C. H. and Amidon, E. L. Electrocardiographic Findings in Forty Four Cases of Trichinosis. *Am. Heart J.*, 16 219 1938
- 52 Gottesman, J., Casten D and Beller A. J. Changes in the Electrocardiogram Induced by Acute Pancreatitis. *J.A.M.A.*, 123 692 1943
- 53 Murphy F D and Livezey M M. Electrocardiographic Changes Simulating Those of Acute Myocardial Infarction in a Case of Perforated Gastric Ulcer. *Am. Heart J.*, 28 533 1944
- 54 Wendkos, M H and Noll J., Jr. Myocarditis Caused by Epidemic Parotitis. *Am Heart J.*, 27 418 1944
- 55 Ziskin, T and Dumas, A G. Observations on the Electrocardiogram in Epilepsy and Comparison with Electrocardiogram in Seizures Following Convulsant Drug Therapy. *J Lab & Clin. Med.*, 27 1249 1942.
- 56 Kline, E. M., Fetterman, J L. and Williams, G H. Electrocardiographic Changes Following Ultrazol Induced Convulsions. *Am Heart J.*, 20 702 1940

- 14 Schmitker, M A The Electrocardiogram in Congenital Cardiac Disease, 1st ed Cambridge, Mass, Harvard University Press, 1940
- 15 Willus, F A, Dry, T J and Reeser, R., Jr Life Expectancy in Conductive Disturbances Affecting the Ventricular Complex of the Electrocardiogram I General Considerations of Bundle Branch Block with Concordant and with Discordant Graphs and the Wide S Wave Pattern, Based on 1611 Cases Arch Int Med, 67 1008, 1941
- 16 Moore, N S and Stewart, H J The Disappearance of Intraventricular Heart-Block Occurring in Uremia Following the Intravenous Injection of Hypertonic Glucose Solutions Am Heart J, 5 469, 1930
- 17 Wolff, L, Parkinson, J and White, P D Bundle Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia Am Heart J, 5 685, 1930
- 18 Wood, F C, Wolferth, C C and Geckler, G D Histologic Demonstration of Accessory Muscular Connections between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex Am Heart J, 25 454, 1943
- 19 Herrick, J B Clinical Features of Sudden Obstructions of the Obstruction of the Coronary Arteries J A M.A., 59 2015, 1912
- 20 Standardization of Precordial Lead Joint Recommendation of the American Heart Association and the Cardiac Society of Great Britain and Ireland. Am Heart J, 15 107, 235, 1938
- 21 Pardee, H E B An Electrocardiographic Sign of Coronary Artery Obstruction Arch Int Med., 26 244, 1920
- 22 Wood, F C, Wolferth, C C and Bellet, S Infarction of the Lateral Wall of the Left Ventricle Electrocardiographic Characteristics Am Heart J, 16 387, 1938
- 23 Thomson, H W and Feil, H Infarction of the Lateral Wall of the Left Ventricle, Pathologic and Electrocardiographic Study Am J Med Sc., 207 588, 1944
- 24 Shaffer, C F Electrocardiographic Study of Lateral Infarction, Proved at Autopsy Am Heart J, 28 39, 1944
- 25 Baer, S and Frankel, H Studies in Acute Myocardial Infarction III Diagnosis and Location of the Infarct by Electrocardiogram Arch Int Med., 73 286, 1944
- 26 Hamman, L Coronary Embolism Am Heart J, 21 401, 1941
- 27 Arenberg, H Traumatic Heart Disease A Clinical Study of 250 Cases of Non-Penetrating Chest Injuries and Their Relation to Cardiac Disability Ann Int Med 19.326, 1943
- 28 Barber, H Electrocardiographic Changes Due to Trauma Brit. Heart J., 4 83, 1942
- 29 Fraser, W A and Myer, T Electrocardiographic Findings Associated with a Gunshot Wound of the Heart New England J Med., 225 286, 1941
- 30 Olm, C B and Hughes, J D Stab Wound of the Heart with Coronary Ligation J Thoracic Surg., 9 99, 1939
- 31 Elkin, D C and Phillips, H S Stab Wound of the Heart. Electrocardiographic Studies of Two Cases J Thoracic Surg, 1 113, 1931
- 32 Solovay, J., Rice, G D and Solovay, H U Electrocardiographic Changes in Stab and Gunshot Wounds of the Heart, with Review of the Literature Ann Int Med., 15 465, 1941
- 33 Rosenbaum, F F, Johnson, F D and Alzamora, V V Persistent Displacement of the RS-T Segment in a Case of Metastatic Tumor of the Heart Am Heart J., 27 667, 1944
- 34 Longcope, W T and Fisher, A W Involvement of the Heart in Sarcoidosis or Besnier-Boeck-Schaumann's Disease J Mt. Sinai Hosp., 8 784, 1942

- 35 Blotner H and Sosman, M. C. X-ray Therapy of the Heart in a Patient with Leukemia, Heart Block and Hypertension. *New England J Med.*, 250 793 1944
- 36 Stewart, H. J. and Bailey R. L. Changes in the Rhythm of the Heart During Resection of the Pericardium in Chronic Constrictive Pericarditis, as Recorded Electrocardiographically. *Am. Heart J.*, 22 169 1941
- 37 Rachmilewitz, M. and Braun K.. The Presence of Electrocardiographic Changes in Nicotinic Acid Deficiency and Their Elimination by Nicotinic Acid. *Am Heart J.*, 27 203 1944
- 38 Beller, S. and McMillan T. M. Electrocardiographic Patterns in Acute Pericarditis: Evolution, Causes, and Diagnostic Significance of Patterns in Limb and Chest Leads. Study of Fifty-Seven Cases. *Arch. Int. Med.*, 61 381, 1938
- 39 Wolff L. Acute Pericarditis Simulating Myocardial Infarction. *New England J Med.*, 230 442 1944
- 40 Findelstein, D. and Klainer M. J. Pericarditis Associated with Primary Atypical Pneumonia. *Am. Heart J.*, 28 385 1944
- 41 Master A. M., Romanoff A. and Jaffe, H. Electrocardiographic Changes in Pneumonia. *Am. Heart J.*, 6 696 1931
- 42 Stewart, H. J. and Heuer G. J. Chronic Constrictive Pericarditis. Dynamics of the Circulation and Results of Surgical Treatment. *Arch. Int. Med.*, 63 504 1939
- 43 McGinn S. and White, P. D.. Acute Cor Pulmonale Resulting from Pulmonary Embolism. Its Clinical Recognition. *J.A.M.A.*, 104 1473, 1935
- 44 Stewart, H. J., Kirk, R. C. and Smith, J. J. Electrocardiographic Changes in Pulmonary Infarction. *New International Clinics 3 Series*, 3 135, 1940
- 45 Love, W. S., Jr., Brugler G. W. and Winslow N. Electrocardiographic Studies in Clinical and Experimental Pulmonary Embolization. *Ann. Int. Med.*, 11 2109 1938.
- 46 Fitz Hugh, T. and Wolferth, C. C. Cardiac Improvement Following Gall Bladder Surgery. *Ann Surg.*, 101 478, 1935
- 47 Ash R., Rubin, M. L. and Rapoport, M. Electrocardiographic Variations in Acute Glomerulonephritis. *Am. J. Dis. Child.*, 67 106, 1944
- 48 Cole S. L. and Bohning A. Electrocardiographic Patterns in Cardiovascular Syphilis. *Am. J. M. Sc.*, 207 317 1944
- 49 Evans, W. and Wright, G. Electrocardiograms in Friedreich Disease. *Brit. Heart J.*, 4 91 1942
- 50 Cushing E. H. Electrocardiographic Changes in Trichinosis. *Am. Heart J.*, 11 494 1936
- 51 Beecher C. H. and Amidon, E. L. Electrocardiographic Findings in Forty-Four Cases of Trichinosis. *Am. Heart J.*, 16 219 1938
- 52 Gottesman, J., Casten, D. and Beller A. J. Changes in the Electrocardiogram Induced by Acute Pancreatitis. *J.A.M.A.*, 123:892 1943
- 53 Murphy F. D. and Lavezey M. M.. Electrocardiographic Changes Simulating Those of Acute Myocardial Infarction in a Case of Perforated Gastric Ulcer. *Am Heart J.*, 28 533 1944
- 54 Wendkos, M. H. and Noll, J., Jr. Myocarditis Caused by Epidemic Parotitis. *Am Heart J.*, 27 418 1944
- 55 Ziskin, T. and Dumas, A. G. Observations on the Electrocardiogram in Epilepsy and Comparison with Electrocardiogram in Seizures Following Convulsant Drug Therapy. *J. Lab. & Clin. Med.*, 27 1249 1942
- 56 Kline, E. M., Fetterman, J. L. and Williams, G. H.. Electrocardiographic Changes Following Metrazol Induced Convulsions. *Am. Heart J.*, 20 702, 1940

- 57 Kline, E M and Fetterman, J L Electrocardiographic Changes Following Electrically Induced Convulsions *Am Heart J*, 24 665, 1942
- 58 Shookhoff, C and Taran, L M Electrocardiographic Studies in Infectious Diseases II Scarlet Fever *Am J Dis Child*, 42 554, 1931
- 59 Roelsen, E Electrocardiographic Studies in Scarlet Fever *Acta medica Scandinavica*, 106 1, 1941
- 60 Hume, W E and Szekely, P Cardiac Involvement in Spirochaetal Jaundice *Brit Heart J*, 6 135, 1944
- 61 Bellet, S and Dyer, W W The Electrocardiogram During and After Recovery from Diabetic Coma *Am Heart J*, 13 72, 1937
- 62 Szekely, P Electrocardiographic Findings in Anemia *Brit. Heart J*, 2 1, 1940
- 63 Stewart, H J, Crane, N F and Deitrick, J E Studies of the Circulation in Pernicious Anemia *J Clin Investigation*, 16 431, 1937
- 64 Hollander, A G and Crawford, J H Roentgenologic and Electrocardiographic Changes in the Normal Heart During Pregnancy *Am Heart J*, 26 364, 1943
- 65 Hamman, L Spontaneous Mediastinal Emphysema *Bull Johns Hopkins Hosp*, 64 1, 1939
- 66 Cohn, A E, Fraser, F R and Jamieson, R A The Influence of Digitalis on the T wave of the Human Electrocardiogram *J Exper Med*, 22 1915
- 67 Stewart, H J and Watson, R F The Effect of Digitalis on the Form of the Human Electrocardiogram, with Special Reference to Changes Occurring in the Chest Lead *Am Heart J*, 15 604, 1938
- 68 Geiger, A J, Blaney, L G and Druckemüller, W H A Quantitative Electrocardiographic Study of Digitalization *Am Heart J*, 22 230, 1941
- 69 Golden, J S and Brams, W A Mechanism of the Toxic Effects from Combined Use of Calcium and Digitalis *Ann Int Med*, 11 1084, 1938
- 70 Stewart, H J The Use of Calcium Chloride Given Intravenously in Congestive Heart Failure *Am Heart J*, 4 646, 1929
- 71 Bower, J O and Mengle, H A K. The Additive Effect of Calcium and Digitalis A Warning, with a Report of Two Deaths *J.A.M.A.*, 106 1936
- 72 Smith, P K, Winkler, A W and Hoff, H E Calcium and Digitalis Synergism The Toxicity of Calcium Salts Injected Intravenously into Digitalized Animals *Arch Int. Med*, 64 322, 1939
- 73 Heimann, H L and Shapiro, B G Effects of Plasmoquin, Arabin and Quinine on the Electrocardiogram *Brit Heart J*, 5 131, 1943
- 74 Stewart, H J, Deitrick, J E. and Crane, N F Studies of the Circulation in Patients Suffering from Spontaneous Myxedema *J Clin Investigation*, 17 237, 1938
- 75 Gordan, G, Soley, M H and Chamberlain, F L Electrocardiographic Features Associated with Hyperthyroidism *Arch Int. Med*, 73 148, 1943
- 76 Evans, W F and Stewart, H J The Effect of Smoking Cigarettes on the Peripheral Blood Flow *Am Heart J*, 26 78, 1943
- 77 Graybiel, A, Starr, R S and White, P D Electrocardiographic Changes Following the Inhalation of Tobacco Smoke *Am Heart J*, 15 89, 1938
- 78 Roth, G M., McDonald, J B and Sheard, C The Effect of Smoking Cigarettes and of Intravenous Administration of Nicotine on the Electrocardiogram, Basal Metabolic Rate, Cutaneous Temperature, Blood Pressure and Pulse Rate of Normal Persons *J.A.M.A.*, 125 761, 1944
- 79 Barker, P S., Johnston, F D and Wilson, F N The Duration of Symptoms in Hypocalcemia *Am Heart J*, 14 82, 1937
- 80 Stewart, H J., and Smith, J J Changes in the Electrocardiogram and

the Cardiac Rhythm During the Therapeutic Use of Potassium Salts. *Am. J. M. Sc.*, 201 177 1941

- 81 Keith N M., Burchell H B and Baggenstoss, A. H. Electrocardiographic Changes in Uremia Associated with a High Concentration of Serum Potassium Report of Three Cases *Am. Heart J.*, 27 1 1944
- 82 Fioc'h C. A and Marchand J F. Cardiac Arrest by the Action of Potassium. *Am. J. M. Sc.*, 206 507 1943
- 83 Stewart, H J., Smith, J J and Milhorat A. T. Electrocardiographic and Serum Potassium Changes in Familial Periodic Paralysis. *Am. J. M. Sc.*, 199 789 1940
- 84 Scherf D and Klotz, S D. Electrocardiographic Changes After Acute Loss of Blood *Ann. Int. Med.*, 20 438, 1944
- 85 Scherf D., Reinstein, H and Klotz, S. D. Electrocardiographic Changes Following Hematemesis in Peptic Ulcer *Rev. Gastroenterol.*, 6 343 1941
- 86 Hartwell, A. S., Burrett, J B., Graybiel, A. and White, P D. The Effect of Exercise and of Four Commonly Used Drugs on the Normal Human Electrocardiogram, with Particular Reference to the T Wave Changes *J. Clin. Investigation*, 21 409 1942
- 87 Evans, W and Hoyle, C. The Effect of Nitrite on the Inverted T Waves in the Human Electrocardiogram *Lancet*, 1 1109 1933
- 88 Stokes, W. Nicotinic Acid in the Treatment of Angina Pectoris. *Brit. Heart J.*, 6 157 1944
- 89 Starr I. Acetyl- $\beta$ -Methylcholine. IV. Further Studies of Its Action in Paroxysmal Tachycardia and in Certain Other Disturbances of the Cardiac Rhythm. *Am. J. M. Sc.*, 191 210 1936.
- 90 Kurtz, C. M., Bennett, J H and Shapiro H H. Electrocardiographic Studies During Surgical Anesthesia. *J.A.M.A.*, 106 434 1936.
- 91 Patterson, J E., Clark T W and Levy R. L. A Comparison of Electrocardiographic Changes Observed During the "Anoxemia Test" on Normal Persons and on Patients with Coronary Sclerosis. *Am. Heart J.*, 23 837 1941
- 92 Evans C. and Bourne G. Electrocardiographic Changes after Anoxemia and Exercise in Angina of Effort. *Brit. Heart J.*, 3 69 1941
- 93 Jones, C. M. Hiatus Esophageal Hernia with Special Reference to a Comparison of Its Symptoms with Those of Angina Pectoris. *New England J. Med.*, 225 963 1941
- 94 Wolferth C. C. and Edeiken, J. The Differential Diagnosis of Angina Pectoris with Special Reference to Esophageal Spasm and Coronary Occlusion. *Pennsylvania M. J.*, 45 579 1942
- 95 Graybiel A and White, P D. Inversion of the T Wave in Lead I or II of the Electrocardiogram in Young Individuals with Neurocirculatory Asthenia, with Thyrotoxicosis in Relation to Certain Infections, and Following Paroxysmal Ventricular Tachycardia. *Am. Heart J.*, 10 345 1935
- 96 Manzer, F and Krause M. The Influence of Fear on the Electrocardiogram. *Brit. Heart J.*, 1-2 271 1939-40
- 97 Stead, E. A., Jr and Warren J V. Clinical Significance of Hyperventilation. The Role of Hyperventilation in the Production, Diagnosis, and Treatment of Certain Anxiety Symptoms. *Am. J. M. Sc.*, 206 183 1943
- 98 Hinshaw H C., Rushmer R. F and Boothby W M. The Hyperventilation Syndrome and Its Importance in Aviation *J. Aviation Med.* June, 1943 p 3
- 99 Barker P S., Shrader L. L. and Ronzoni E. The Effects of Alkalosis and of Acidosis upon the Human Electrocardiogram *Am. Heart J.*, 17 169 1939

# THE DIFFERENTIAL DIAGNOSIS OF PEPTIC ULCER

I W HELD, M D \*

## DIFFICULTIES IN DIAGNOSIS OF INTRA-ABDOMINAL DISEASE

THE difficulty offered in the differential diagnosis of intra-abdominal diseases, particularly of the digestive tract, is too well known to warrant extensive discussion. As compared to diagnosis of diseases of any other part of the body, it more frequently involves a decision between medical or surgical treatment as the method of necessity, which is of the utmost importance to the patient as well as to the physician. Such decisions must be made not only in acute diseases of the digestive organs, but also in diseases of a chronic nature.

Gaithes<sup>1</sup> expressed his keen appreciation of this problem in the following manner: "Abdominal diagnosis resembles in various details its fellow science archaeology, both find their greatest triumphs in tracing hidden levels, but here they diverge. The farther the archaeologist delves, the greater his enlightenment, while the farther the abdominal diagnostician seeks and the wider and deeper his experience the more clearly he realizes how large is the number of syndromes presenting atypical, puzzling, frequently baffling symptoms."

Among the outstanding reasons for the difficulty in the diagnosis of diseases of the digestive tract is the fact that the parasympathetic and sympathetic nervous system and the autonomous innervation by the Auerbach and Meissner plexuses are intimately interwoven with the function of the digestive organs. Disturbance in the function of one organ may strongly simulate disturbed function of another organ and thus render impossible the clinical determination of the actual site of the disorder.

A second prominent factor is that even perfectly healthy digestive organs may, as a result of purely functional derangement, simulate real organic disease.

Thirdly, prolonged functional disturbance of one or another digestive organ may eventually lead to actual organic changes. The transition may be very gradual until suddenly a catastrophe due to organic changes may take place. Since the afflicted individual had suffered only functional disturbances without any demonstrable lesion for many years, the physician who was somewhat indifferent to the existing syndrome is shocked by the sudden conversion of a psychic state into a real somatic state. The organs of the digestive tract are disturbed by psychic influences more readily than any other organ,<sup>25</sup>

---

\* Attending Physician, Beth Israel Hospital, New York City, Formerly Clinical Professor of Medicine, New York University College of Medicine

has been demonstrated by many physiologists and particularly by Wolf and Wolff.<sup>2</sup>

A fourth factor is existing disease in one organ of the digestive tract which may affect the function of other organs and eventually lead to organic changes in them. The frequency with which peptic ulcer, gallbladder disease and appendicular disease are encountered by the surgeon and the pathologist corroborates this fact, and led Roessle to speak of peptic ulcer as a disease secondary to chronic gallbladder or appendicular disease.

Our discussion of this topic will be confined chiefly to peptic ulcer with atypical symptoms and to chronic appendicular disease which may so simulate peptic ulcer as to make differential diagnosis difficult, if not impossible.

#### PEPTIC ULCER WITH ATYPICAL SYMPTOMS

Prior to Moynihan peptic ulcer was rarely diagnosed ante mortem. He was one of the earliest to emphasize the diagnosticable aspect of ulcer, particularly of the duodenum, and at one time thought that the history is of primary importance, the physical examination secondary. After extensive surgical and pathological experience, he came to realize that disease in the ileocecal region, and even such thoracic conditions as coronary artery disease, may simulate peptic ulcer. So he reversed himself completely and stated that even in cases of gastric hemorrhage one must often think "away from the stomach" when judging the cause of the catastrophe, for the lesion might be in other intra-abdominal organs. This last remark seems exaggerated but it is true on rare occasions, as will be illustrated below.

Braithwaite<sup>3</sup> created the terms "gastroileac syndrome" and "ileo-gastric syndrome." By the former he meant a clinical condition where the disease lies in the stomach and the patient's symptoms are referred to the ileocecal region, by the latter he intended to signify pathologic change in the ileocecal region with the symptoms referable to the gastric area. It has been our experience that when the primary lesion, peptic ulcer in particular, is in the stomach proper, the symptoms are seldom referred to the appendicular region. If lower abdominal symptoms do exist, actual disease coexists in the ileocecal region. On the other hand, if the primary affection, with the exception of terminal ileitis, is in the ileocecal region, the symptoms are often referable to the epigastrium, even simulating fully those of gastric or duodenal ulcer.

*Ulcer in the Asthenic Person*—Some years ago Gross and Held<sup>4</sup> cited a number of causes for atypical symptoms of ulcer of the ventriculum. The first of these was sensitiveness of the individual. In the asthenic person functional or nervous complaints may be so in the foreground as to mask entirely symptoms due to the ulcer. At one time severe headaches prevail, at another cardiovascular instability, or abdominal



# THE DIFFERENTIAL DIAGNOSIS OF PEPTIC ULCER

I W HELD, MD \*

## DIFFICULTIES IN DIAGNOSIS OF INTRA-ABDOMINAL DISEASE

THE difficulty offered in the differential diagnosis of intra-abdominal diseases, particularly of the digestive tract, is too well known to warrant extensive discussion. As compared to diagnosis of diseases of any other part of the body, it more frequently involves a decision between medical or surgical treatment as the method of necessity, which is of the utmost importance to the patient as well as to the physician. Such decisions must be made not only in acute diseases of the digestive organs, but also in diseases of a chronic nature.

Gaithes<sup>1</sup> expressed his keen appreciation of this problem in the following manner: "Abdominal diagnosis resembles in various details its fellow science archaeology, both find their greatest triumphs in tracing hidden levels, but here they diverge. The farther the archaeologist delves, the greater his enlightenment, while the farther the abdominal diagnostician seeks and the wider and deeper his experience the more clearly he realizes how large is the number of syndromes presenting atypical, puzzling, frequently baffling symptoms."

Among the outstanding reasons for the difficulty in the diagnosis of diseases of the digestive tract is the fact that the parasympathetic and sympathetic nervous system and the autonomous innervation by the Auerbach and Meissner plexuses are intimately interwoven with the function of the digestive organs. Disturbance in the function of one organ may strongly simulate disturbed function of another organ and thus render impossible the clinical determination of the actual site of the disorder.

A second prominent factor is that even perfectly healthy digestive organs may, as a result of purely functional derangement, simulate real organic disease.

Thirdly, prolonged functional disturbance of one or another digestive organ may eventually lead to actual organic changes. The transition may be very gradual until suddenly a catastrophe due to organic changes may take place. Since the afflicted individual had suffered only functional disturbances without any demonstrable lesion for many years, the physician who was somewhat indifferent to the existing syndrome is shocked by the sudden conversion of a psychic state into a real somatic state. The organs of the digestive tract are disturbed by psychic influences more readily than any other organ, as

---

\* Attending Physician, Beth Israel Hospital, New York City, Formerly Clinical Professor of Medicine, New York University College of Medicine

has been demonstrated by many physiologists and particularly by Wolf and Wolff<sup>3</sup>

A fourth factor is existing disease in one organ of the digestive tract which may affect the function of other organs and eventually lead to organic changes in them. The frequency with which peptic ulcer, gallbladder disease and appendicular disease are encountered by the surgeon and the pathologist corroborates this fact, and led Roessle to speak of peptic ulcer as a disease secondary to chronic gallbladder or appendicular disease.

Our discussion of this topic will be confined chiefly to peptic ulcer with atypical symptoms and to chronic appendicular disease which may so simulate peptic ulcer as to make differential diagnosis difficult, if not impossible.

#### PEPTIC ULCER WITH ATYPICAL SYMPTOMS

Prior to Moynihan peptic ulcer was rarely diagnosed ante mortem. He was one of the earliest to emphasize the diagnosticable aspect of ulcer, particularly of the duodenum, and at one time thought that the history is of primary importance, the physical examination secondary. After extensive surgical and pathological experience, he came to realize that disease in the ileocecal region, and even such thoracic conditions as coronary artery disease, may simulate peptic ulcer. So he reversed himself completely and stated that even in cases of gastric hemorrhage one must often think "away from the stomach" when judging the cause of the catastrophe, for the lesion might be in other intra-abdominal organs. This last remark seems exaggerated but it is true on rare occasions as will be illustrated below.

Braithwaite<sup>3</sup> created the terms "gastroileac syndrome" and "ileo-gastric syndrome." By the former he meant a clinical condition where the disease lies in the stomach and the patient's symptoms are referred to the ileocecal region, by the latter he intended to signify pathologic change in the ileocecal region with the symptoms referable to the gastric area. It has been our experience that when the primary lesion, peptic ulcer in particular, is in the stomach proper, the symptoms are seldom referred to the appendicular region. If lower abdominal symptoms do exist, actual disease coexists in the ileocecal region. On the other hand, if the primary affection, with the exception of terminal ileitis, is in the ileocecal region, the symptoms are often referable to the epigastrium, even simulating fully those of gastric or duodenal ulcer.

**Ulcer in the Asthenic Person**—Some years ago Gross and Held<sup>4</sup> cited a number of causes for atypical symptoms of ulcer of the ventriculum. The first of these was sensitiveness of the individual. In the asthenic person functional or nervous complaints may be so in the foreground as to mask entirely symptoms due to the ulcer. At one time severe headaches prevail, at another cardiovascular instability, or abdominal

disturbances Only close questioning elicits symptoms suggestive of peptic ulcer in some cases Such individuals are vagotoniacs or vago-sympathicotoniacs (Eppinger and Hess) It is commonly known that in these people the functional disturbance can precede the organic disturbance by many years Gastric hemorrhage and even perforation may suddenly occur without any warning symptoms The disturbances of gastric function may vary Secretory disorders may be in the foreground, these are persistent pyrosis, regurgitation of sour fluid which awakens the patient at night, numbness of the gums due to the excess acid saliva, marked redness of the tongue or erosion of the pharynx, mouth and gums, and dullness of the teeth In other cases and/or occasionally in the same patient, sensory symptoms are outspoken The pain however, is not the hunger type or periodically recurring two or three hours after meals, it is persistent

When peptic ulcer is present, pain is usually elicited on deep pressure over the epigastric region or right hypochondrium However, the asthenic patient often finds relief by exerting deep pressure over that area himself Superficial pain, which may radiate to the intercostal region, is usually present, undoubtedly a vagosympathicotonic phenomenon As a rule, disease without pain except on deep pressure is organic, superficial pain is experienced by the sympathicotonic type of person

Very often the asthenic patient will show marked motility disturbance at certain periods Although there is no demonstrable roentgenologic lesion in the stomach or duodenum, there may be transient marked delay in the emptying of the stomach, or marked hyperperistalsis simulating pyloric stenosis Reexamination a day or two later may reveal normal emptying time of the stomach In some cases nausea so dominates every other complaint that it is clinically difficult to determine whether or not the cause is duodenal irritation on the basis of ulcer Boldyreff demonstrated physiologically that excess acid secretion causes irritation of the duodenum and nausea

In some instances, although pyloric stenosis is not demonstrable, nausea may be temporarily relieved by vomiting Riegel therefore described a "vomiting type of peptic ulcer" It is important to point out that he did not make the diagnosis of ulcer on the basis of clinical observations, but rather on the postmortem finding of ulcer in patients who had died of an intercurrent disease

Secretory, sensory and motility disturbances may occur at different times in the same individual, thus adding to the confusion and causing such individuals to be considered as hypochondriacs The present improved methods of diagnosis can guard the physician against such an error and prevent the further progress of the disease involving serious consequences

**Ulcer in the Hypersthenic Individual**—In contradistinction to the hypersensitive type occurring in asthenic individuals, there is the hyper-

sthenic individual who is usually hyposensitive and minimizes his symptoms. Sudden hemorrhage or even perforation may mark the first alarming symptom because the patient may have been allaying his pains by the use of alkalies. Close questioning after the hemorrhage may disclose the frequent use of bicarbonate of soda or some other proprietary drug.

The *mode of living* of the ulcer patient frequently contributes toward masking the existence of the disease. Some individuals exercise extreme denial of food, others eat to excess. A patient of the former group, after having responded to treatment following a hemorrhage, may continue to observe his diet to such an extreme that undernutrition, avitaminosis and marked enteroptosis may result. His symptoms eventually become unrelenting—a gnawing sensation in the epigastrium, plethoric patient who frequently is also a heavy smoker and a hard and myalgic pains in various parts of the body due to avitaminosis and anemia.

The second group, those who eat excessively, is exemplified by the plethoric patient who frequently is also a heavy smoker and a hard worker. The patient may suffer intermittent attacks of epigastric pain and the moment his symptoms subside he again partakes of large quantities of food, often regardless of quality, and even indulges in alcohol. Finally the condition becomes so aggravated that the pain is persistent. We had two such cases in a pair of brothers. Both of them developed carcinoma of the pylorus after many years. One brother had a gastroenterostomy, with three or four comfortable years postoperatively before carcinoma developed. The other was not operated on for ulcer. He later also developed carcinoma. After gastric resection he lived five years and eventually died from metastatic carcinoma of the liver.

The following is an illustration of a hypersthenic individual with extremely atypical ulcer symptoms.

A man, aged 45 years, gave a history of fifteen years' duration of attacks of pain in the upper abdomen terminating in nausea and vomiting which occurred only when a change in the weather took place. When the weather cleared he could eat almost everything without ill effects, but rain, snow or cloudy weather would cause recurrence of his gastric symptoms. X-ray examination showed a normal stomach; the first portion of the duodenum likewise did not show any characteristic abnormality of ulcer. The sole roentgenologic abnormality consisted of a small six-hour residue in the stomach with the small intestines almost empty and the entire colon filled, despite the fact that the stomach was hypertonic and emptied rapidly during the early part of digestion. These were indirect signs of duodenal ulcer. Fluoroscopically there was no tender area over the epigastrium. The gastric acidity was normal.

After several weeks of treatment on the basis of ulcer the patient failed to improve and repeated x-ray examination revealed similar insignificant findings. Because of his long suffering he decided to submit to operation. We hesitated about advising surgery because the x-ray findings were meager and the symptoms atypical. Ulcer on the posterior wall of the duodenum was found and gastroenterostomy without resection was performed. He has been entirely symptom free for a number of years.

Although reports of ulcer sensitivity to weather have appeared in the literature, we feel that this case was singular in that the patient's pain was so severe that he insisted on an operation

**Associated Gastric Catarrh**—It is not uncommon to find that the symptom complex of peptic ulcer is effaced by an associated gastric catarrh. We are not in favor of the concept that catarrh precedes ulcer,<sup>5</sup> but do agree that in some individuals where periodic pylorospasm causes retention, or the progress of the ulcer causes gastric retention, or where associated atony of the stomach is responsible for the retention, eventually gastric catarrh may develop. Such catarrh may be associated with either sub- or anacidity or hyperacidity. In these cases epigastric fullness or distress after meals, loss of appetite, nausea and extreme dryness in the mouth, coated tongue and bad taste in the mouth predominate. In other cases of this nature, pyrosis is persistent and the patient regularly resorts to the use of bicarbonate of soda or some other proprietary alkali for relief. The history will occasionally disclose typical ulcer symptoms several years previously. In these cases of gastric retention out of proportion to the real organic changes in the ulcer proper, the patient may improve temporarily with gastric lavage, antispasmodics and careful dieting. However, in most instances the symptoms recur, necessitating surgical intervention. Subtotal gastrectomy usually brings about curative results. A patient who refuses operation may have many years of fair comfort by submitting to frequent gastric lavage—for the first week, daily, for the next two months, two or three times a week.

Whereas it is true that, with the aid of the diagnostic methods at our disposal, particularly x-ray, one can establish the diagnosis in the vast majority of cases of peptic ulcer, it is equally true that in the absence of a peptic ulcer history and especially when the patient gives a confusing, vague history more indicative of neurosis than of organic disease, we often forego the x-ray examination and may miss the diagnosis.

**Diagnosis Obscured by the Presence of Other Organic Disease**—The following cases serve to illustrate how other organic disease in a peptic ulcer patient may greatly hamper the diagnosis of ulcer.

In one case of arrested pulmonary tuberculosis the patient was an extremely neurotic individual who had vague gastric complaints. Because of the existing tuberculosis and marked nervousness the diagnosis of duodenal ulcer was not suspected until sudden perforation of the ulcer necessitated immediate operation. Fortunately he recovered after a preliminary operation of suturing the ulcer, without resection, and is now comfortable after six years.

Another case is one of tight mitral stenosis with gastric complaints of many years' duration. The patient was eventually admitted to the Beth Israel Hospital in a state of congestive heart failure and he succumbed. At postmortem, in addition to the chronic valvular disease, a chronic duodenal ulcer was found.

An extremely atypical case is that of a patient (an artist) who for more than twenty years had vague gastric complaints without any symptoms suggestive of ulcer. He had a very marked epigastric hernia for which we advised repair but the patient refused to submit to surgery. For the last ten years he drank large quantities of alcohol and developed alcoholic neuritis. Under vitamin D treatment and withdrawal of the alcohol, he improved. However he reverted to alcoholic excesses and developed cirrhosis of the liver. He was admitted to the Beth Israel Hospital with extreme ascites, and shortly before death had a gastric hemorrhage. A ray examination of the esophagus had failed to reveal suspected varices as the origin of the bleeding. Autopsy showed, in addition to cirrhosis of the liver that a chronic duodenal ulcer was the source of the hemorrhage.

The relatively frequent presence of gastric or duodenal ulcer in cases of *cirrhosis of the liver* was noted by Patek and Ratnoff<sup>6</sup>

*Pyloroduodenal adhesions* or *gallbladder-duodenal adhesions* secondary to ulcer produce a misleading history. In such cases pain in the upper abdomen, radiating to the right side and right shoulder, and periodic attacks of severe epigastric pain due to pylorospasm may so simulate gallbladder disease that the diagnosis of duodenal ulcer is entirely effaced. In many such patients the gallbladder fails to concentrate the dye, adding further to the masking of ulcer symptoms. The x-ray findings and all symptoms are attributed to gallbladder disease. When the symptoms become so aggravated that surgery becomes essential, the lesion is found to be in the duodenum and the gallbladder is found to be perfectly normal.

The *ileogastric syndrome* (Braithwaite), when the disease is confined to the ileocecal region and causes reflex gastric symptoms, is a well established fact. A number of affections in the ileocecal region give rise to reflex gastric symptoms, such as tuberculous adenitis confined to the ileocecal region, or nonspecific adenitis where large calcified glands of a nonspecific nature (the remains of either an acute mesenteric adenitis or some chronic inflammatory condition of the cecum or colon) are present both in the ileocecal region and often in the right side of the abdomen. Also reflex gastrointestinal symptoms may occur in connection with ileitis as described by Crohn, Ginsberg and Oppenheimer, or in connection with chronic pelvic disease such as pelvic cellulitis or disease of the adnexa.

#### CHRONIC APPENDICITIS SIMULATING PEPTIC ULCER

None of the conditions already named ever cause gastric disturbance simulating fully gastric or duodenal ulcer. Chronic appendicular disease is the only pathological condition of the ileocecal region which may fully simulate peptic ulcer.

**Chronic Appendicular Disease—a Clinical Entity**—Many internists and surgeons today regard chronic appendicular disease as a nonexistent entity. That controversial group bases its argument on the fact that often, following appendectomy, the patient will continue to have the

same symptoms as before operation We strongly believe that in such cases there was a mistaken diagnosis, as in the recurrence of so-called gallbladder symptoms after cholecystectomy, where there has been neither serious disease of the gallbladder nor gallstones Every healthy organ must possess some function of greater or lesser importance, and its removal is therefore not only not beneficial but may be harmful On the other hand, both internists and surgeons encounter a large number of cases in which a definite clinical and roentgenologic picture of appendicular disease indicates surgery, and the removal of the appendix is extremely beneficial Such cases may have an associated pylorospasm or pyloritis, or a small erosion may exist in the pyloro-duodenal region which could not be demonstrated roentgenologically or surgically, but which was in need of medical care after the appendectomy

Mention must be made here of the work of Moynihan, Rolleston, Deaver, George D Stewart, Gibson (New York Hospital) and the recent work of M Behrend<sup>7</sup> who were responsible for the establishment of the clinical entity of chronic appendicular disease

**Anatomical Considerations**—It may not here be amiss to review the anatomy of the appendix in general The appendix presents a small lined pouch attached to the tip of the cecum by its vascular and lymphatic supply which, in case of infection, spreads the noxious influence of the diseased appendix not only to the immediate neighboring viscera but also to the most distant parts of the body In view of these facts a pathological appendix becomes an unusual menace The appendix varies in length from 5.5 cm to an extreme length of 28 cm, is longer in young individuals than in those of later life The inner lumen is connected to the cecum by a reduplication of the folds of mucous membrane, described by Gerlach and known as the Gerlach valve

Contents passing from cecum into appendix and from appendix into cecum meet with no resistance unless the position of the appendix in relation to the cecum is such that communication of the contents between the two organs is not possible or in cases where the connection between them is pathologically obliterated Normally the passage of cecal contents into the appendix is very rapid It was shown experimentally that if lycopodium seeds are introduced into the colon by means of an enema it reaches the appendix within fifteen minutes Its shape and peristaltic activity indicate that it has the structure and function of the colon Even normally the appendix may contain some fecal matter, according to Aschoff, in about 60 per cent of cases Roentgenologic studies have demonstrated beyond doubt that a normal appendix fills and empties and changes its position and contour Conclusions may be reached that a diseased appendix quickly loses its elasticity and contractility, hence activity becomes diminished and the appendix may not be able to empty its contents and alter its shape and

position Persistence of dry fecal material and fecal stones in the appendix is an indication of disease Fecal matter may become so hardened as to form definite fecaliths which in turn may erode its mucous membrane and form a source of chronic erosion

The *blood supply* to the appendix is furnished by the ileocolic artery and is carried away by the ileocolic vein into the mesenteric vein This is important to point out because in case of appendicular disease the infectious material may reach the liver by way of the ileocolic vein and mesenteric vein, and give rise to dangerous consequences—thrombophlebitis of the portal vein and liver abscess Also, this furnishes an explanation for adhesions in cases of chronic appendicular disease, which may spread from the ileocecal region to the liver and cause enlargement of the liver and clinical symptoms pointing to disease in the right hypochondrium

The *lymphatics* form a meshwork in the submucosa through which a true connection between the lymphatic vessels, the mesentery and the peritoneum takes place These empty partially into the glands lying at the ileocecal angle and partially between the layers of the mesentery and its communicating glands Enlarged inflammatory glands may therefore occasionally be found in the vicinity of the cecum and ascending colon in some cases of chronic infection of the appendix The lymphatic vessels pass from the ascending colon and ileum to the upper surface of the liver and the ligament connecting it to the diaphragm, thus forming a communication between the lymphatics of the appendix and the subphrenic space, accounting for the existence, in some chronic cases of subphrenic adhesions or adhesions between the diaphragm and liver, and in acute cases of subdiaphragmatic abscess There is no lymphatic connection between the female generative organs and the appendix It had at one time been thought that affections of the generative organs could result secondary to appendicitis by direct extension through the lymphatics.

The *nerve supply* of the appendix is derived from the sympathetic fibers of the mesenteric plexus The numerous branches and nerves connecting with the nerve fibers of the gastrointestinal tract explain the fact that pains in chronic appendicitis may spread over all parts of the abdomen At times the ileofemoral nerve connects with the nerve supplying the appendix, in which instances pain associated with a pathological appendix may spread to the scrotum and to the right side of the thigh Under rare conditions the mucous membrane may atrophy after middle life leading to total or partial obliteration of the appendix The narrowing or complete occlusion of the lumen as well as the complete atrophy of the mucous membrane of the appendix is in a great majority of cases, a result of a previous inflammation which had led to fibrous tissue formation Aschoff demonstrated that before 10 years of age the appendix is obliterated in about 66 per cent of cases, up to 20 years of age, in 12 per cent, up to 30 years 20 per cent,



after 40 years, 28 per cent, after 50 years, 42 per cent, and after 60 years, 14 per cent

**Pathology**—The appendix has offered unusual opportunity for pathological study because it has been removed by surgeons during every possible stage of disease. The fact that the chronically diseased appendix is the result of a previously existing acute appendix is universally accepted. The pathological changes in a chronically diseased appendix depend upon the damage done during the acute stage plus the repeated recurrent attacks resulting from the infectious agent lodging in the organ. In order, therefore, to appreciate what pathological changes can take place in a chronically diseased appendix a few remarks about the changes in the acute stage are necessary.

In many instances, during the acute attack only the superficial epithelium of the distal part of the appendix is destroyed. The defect in the epithelium becomes covered with a fibrinous leukocytic exudate. This early stage can only be seen if the appendix is removed within a few hours after the attack. As a rule, such a stage progresses into a more complicated one. The infection penetrates into the grooves of the mucous membrane and thence often to the serous membrane of the appendix where it forms a leukocytic and later a fibrinous exudate. Aschoff applied the term "appendicitis phlegmonosa ulcerosa simplex" to this stage. If the process begins to recede the superficially destroyed mucous membrane together with the adhesions of the folds of the mucous membrane lead to stenosis, atresia and eventually to complete obliteration of the appendix. When it spreads to the serosa, adhesions to the ileum, cecum or even—depending on the length of the appendix—to distant organs like the generative organs, or to the liver, kidney, urinary bladder, hepatic flexure, spleen or sigmoid may result. True suppuration even to the point of abscess formation may take place in the lumen of the appendix, reach the serosa and become so encapsulated by fibrous tissue that it remains the source of chronic infection without giving rise to immediate surgical intervention.

The question whether a fecal stone may be present in a normal appendix or be the result of infection of the appendix, disabling it from ridding itself of the fluid fecal material and so causing fecal stone, is also a matter of considerable discussion. Aschoff maintains that fecal stone is usually superimposed upon an infection of the appendix. From the clinical standpoint it is important to remember that, although in some cases a fecal stone may be found in the appendix postmortem in cases in which the history does not point to appendiceal disease, a fecal stone is undoubtedly an indication of disturbed peristalsis of the appendix and is frequently the cause of appendicular colic.

In summation, changes in the chronic appendix may be those of stenosis, induration of the walls of the appendix, retention of mucus, fecal masses and fecal stones, and kinking by means of adhesions. These changes necessarily give rise to a varied clinical picture. In addi-

tion, the mesentery of the appendix is often contracted due to adhesions which invade the nerves and give rise to considerable pain, and occasionally forming real neuromas. In normal or obliterated appendices Maresch found distant neuromas which he attributes to involvement of the plexus of the submucosa by fibrous tissue, and which may give rise to considerable pain. In a few such cases in which operation was done at the Beth Israel Hospital, the pathologist, Dr. Plaut, demonstrated neuroma of the appendix. The process may extend to the wall of the cecum causing a moderately contracted and spastic cecum or it may cause catarrh of the mucous membrane and dilatation. At times pathological changes in the appendix may be the cause of diverticuli.

Chronic appendicular disease may also be caused by worms lodged in the appendix. Cecil and Bulkley described a characteristic form of appendicitis due to parasites, which consists of catarrhal inflammation with small hemorrhages. Actinomycosis as well as cancer may affect the appendix without affecting other organs. This is also true of periarteritis nodosa. Mucous substance may be found in the appendix and its mesentery and may form a tumor of considerable size, or the gelatinous contents may break through the appendix into the peritoneum or the appendix may undergo malignant degeneration.

**Symptomatology**—The symptoms of chronic appendicitis vary. In a small number of cases diagnosis is fairly easy because of a history of one or more recurrent attacks. In many cases, however, such history is lacking either because the attack occurred in early childhood and passed from memory and caused no later complications, or the attack in the adult may have been so mild that the patient did not consult a physician. However, mere tenderness over the ileocecal region with some vague gastric symptoms does not justify the diagnosis of chronic appendicular disease without a very careful physical and x-ray examination. It has been well established that a diseased appendix can produce definite symptoms of gastric or duodenal disorder with hardly any localized symptoms. Moynihan rightly termed these symptoms "appendicular dyspepsia," and Sir Humphrey Rolleston divided the symptoms of chronic appendicitis into four groups, namely (1) reflex, (2) mechanical, (3) toxic, and (4) infective (discussed in detail by Held in 1924).<sup>8</sup>

In this communication we are chiefly concerned with the *reflex symptoms* particularly referable to symptoms simulating gastric or duodenal ulcer. These reflex phenomena may manifest themselves in secretory disturbance of the stomach in the form of hypersecretion and hyperacidity, chiefly of alimentary character, with symptoms of pyrosis, regurgitation of acid secretion and vomiting, in some cases there may even be continuous hypersecretion. The secretory disturbance can manifest itself by excessive mucus in the colon, giving rise to colica mucosa. Or it may spread to the salivary glands and cause

increased salivation Urinary symptoms may be the prominent complaint, particularly frequent micturition without increase of the quantity of the urine, which is the result of gastric hyperacidity with diminished acid in the urine or of alkalinity of the urine, either causing irritation of the urinary bladder

When *motor disturbances* are in the foreground, there is distress in the epigastrium, epigastric pressure shortly after meals, persistent belching and regurgitation of sour fluid, peristaltic unrest in the upper quadrant and in the cecum, rigidity of the cecum and of the rectus muscle overlying the cecum

More rarely, the motor disturbance manifests itself in atony of the stomach characterized by a splashing sound over the stomach and cecum and other signs of atony in the cecum such as persistent gurgling, more marked five or six hours after meals

If *sensory disturbances* predominate, the patient complains of persistent pain in the epigastric region often radiating to the thorax, but an indication of appendicular involvement is the fact that pressure over the appendicular region causes pain in the epigastrium (Aaron sign), and Head's zone is more marked over the appendicular region

In a patient who has both marked secretory and sensory disturbances, the differential diagnosis between ulcer and chronic appendicular disease is practically impossible It is quite likely that in such a case superficial gastric erosions may have resulted from the persistent hypersecretion, and is responsible for the pain

The following case histories are illustrative of chronic appendicitis simulating peptic ulcer

A physician had vague gastrointestinal symptoms for a long time He used alkalis frequently for relief of epigastric distress One afternoon, while in the operating room, he had a severe gastric hemorrhage After six weeks, during which time he was given several transfusions, he decided to submit to surgery Operation revealed a normal stomach and duodenum but marked adhesions were found around the ileocecal region and also a chronically inflamed appendix The patient made a complete recovery and remained entirely symptom-free

A 21 year old male suffered a severe gastric hemorrhage as the only symptom of disease The family history revealed that his mother had been operated on for ulcer and his sister had typical symptoms of peptic ulcer Several weeks after recovery from the hemorrhage, operation was performed, stomach and duodenum were entirely normal and a chronically diseased appendix was found

According to statistics from the Mayo Clinic, gastric hemorrhage occurs in about 2 per cent of cases of chronic appendicitis, the stomach being entirely normal

Cases similar to the above are cited in the literature on the subject Whereas hemorrhage in the peptic ulcer case is usually controlled, unless there is a pancreatoduodenal rupture, in cases of chronic appendicitis the hemorrhage tends to persist, causing severe secondary

anemia and checked only after repeated transfusions. In acute appendicitis marked hyperemia of the gastric mucosa with capillary oozing or thrombi is responsible for bleeding. However, in chronic appendicitis hemorrhage is a rare phenomenon and the underlying cause is unexplainable.

The symptoms of gastric or duodenal ulcer resulting from chronic appendicitis without bleeding are not uncommon. An important point in the differential diagnosis is the fact that when the extragastric disease is chronic appendicitis there is no periodicity of symptoms. The patient may have some comfortable days, but he is afflicted with symptoms practically most of the year. Patients who because of persistent pyrosis become addicted to large doses of alkalis eventually develop associated gastric catarrh. Very often one encounters in such cases the transient symptoms due to pylorospasm or irritation of the duodenum which causes true pyloritis and often duodenitis. The surgeon operating in such cases occasionally finds an unexplainable thickening of the pylorus which is undoubtedly due to repeated attacks of pylorospasm causing some hypertrophy of the pylorus. Removal of the appendix may produce relief temporarily. However, resumption of errors in diet or exposure to emotional strain will lead to recurrence of the symptoms. One may even clinically suspect that the persistent pyloritis or duodenitis may later lead to true ulcer formation of the pylorus or duodenum if the patient is not treated both dietetically and emotionally on the basis of ulcer after the appendectomy. Not infrequently, after removal of a chronically diseased appendix although the surgeon made a very careful search during operation and found no ulcer, several months later the patient has been known to return with ulcer symptoms, and x-ray has revealed the presence of a gastric or duodenal ulcer. In explanation one may assume that a previously existing irritation of pylorus or duodenum was the focus for the development of the ulcer.

**Direct Physical Signs**—The diagnosis of chronic appendicitis is of the utmost importance because if the appendix is diseased the only possible cure is the removal of the organ. From the symptoms alone it is very difficult to establish a positive diagnosis. Some of the leading physical signs which aid in diagnosis are the following:

1. Tenderness in the ileocecal region, especially on deep pressure.
2. Rigidity of the right rectus muscle which is often present in chronic cases also. This is especially marked if there are pericecal adhesions.
3. Pressure in the appendicular region causing pain in the epigastrium (Aaron's sign).
4. Tenderness over the ileocecal region when the colon is inflated with air (Bastedo sign).
5. Rieder sign which consists of tenderness over the appendicular region on rectal examination.

6 Pain over the appendicular region if deep pressure is exercised over the left side at a point corresponding to McBurney's point on the right side

Within our own experience we have observed many cases in which a chronically diseased retrocecal appendix gives rise to spontaneous pain in the right loin. Upon exertion of pressure over the point of spontaneous pain, referred pain is experienced in the appendicular region.

**Roentgenologic Examination—Its Importance**—Careful clinical and roentgenologic examinations are of primary importance in determining whether a diseased appendix is the actual and sole cause of the ulcer symptoms. The clinical examination alone will often not be conclusive, so that roentgenography is the deciding means of ruling out gastric or duodenal ulcer. We need not go into detail about the x-ray phenomena of gastric or duodenal ulcer, but suffice it to say that if thorough roentgenologic study is done, including the mucous membrane of the stomach and the first and second portions of the duodenum, one can determine with a fair degree of certainty the presence of an ulcer. This is particularly true of duodenal ulcer where the x-ray diagnosis is conclusive in 95 per cent of cases. Mucous membrane studies are an outstanding aid in the diagnosis of gastric ulcer.

X-ray study of the motor phenomena of the stomach and duodenum is especially valuable when gastric or duodenal symptoms are due to some extragastric factor, particularly chronic appendicitis. Quite often one encounters in such cases persistent pylorospasm indicated by the marked narrowing of the pylorus due to spasm of the sphincter pylori. In the course of fluoroscopy, or during the taking of films, fifteen to twenty minutes may elapse before some contrast reaches the duodenum. At times partial gastropasm is encountered. In other instances the duodenal irritation is manifested by either its spasticity or slight irregularity both on the lesser and greater curvatures. Such phenomena are usually transient, they are evident in the earlier part of digestion, but disappear entirely within an hour or two and a good outline of the duodenum is obtainable. Other x-ray evidence of motor disturbance consists of four, five and six hour residue in the stomach in cases of chronic appendicitis.

**Direct Roentgenologic Signs**—From the roentgenologic standpoint it is important to observe carefully the filling and emptying of the appendix, its shape, position, mobility and motility, spasm, tenderness under the fluoroscope, and the presence of concretions.

The patient is to be examined, films taken after four, six, twenty-four and forty-eight hours and if the appendix remains filled, as late as seventy-two hours. A normal appendix empties and fills repeatedly during the course of the examination. If the appendix remains persistently filled there is reason to attribute pathological significance to it.

The abnormal appendix may be shortened, thick, at times as wide as it is long, the shape and position not altering throughout the entire course of the examination. The shortness and thickness do not necessarily indicate that the diseased appendix is not longer than seen on the roentgenogram. But it does indicate that the lumen of the appendix is obliterated in some of its parts and therefore only the upper part fills with the contrast substance.

An abnormal appendix may be unusually long, fixed and persistently filled. The position of the appendix varies even physiologically, and a malposition of the appendix is of pathological importance if it remains fixed and is tender when examined fluoroscopically. Certain malpositions of the appendix, however, invariably indicate pathologic changes, namely: if the appendix is pulled to the left side or low down into the pelvis, or to the region of the urinary bladder, or up to the retrocecal region. The presence of concretions indicates that the appendix cannot successfully empty itself of its contents, and that there is disease of its mucous membrane. A persistently kinked, coiled appendix that does not alter its shape is likewise an indication of disease.

There are also other direct signs which are the result of adhesions caused by a diseased appendix. These are either a very low or very high position of the cecum, restricted mobility of the cecum, pulling of the sigmoid to the right or pulling of the cecum to the left. At times the cecum and the appendix are so pulled to the left by adhesions that the patient has pain over the left lower quadrant and the surgeon in reality unravels a so-called left-sided appendix. Sometimes the appendix, by adhesions, spreads to the transverse colon pulling the transverse colon downwards and causing kinking of the hepatic flexure. The adhesions may cause a matting together of the ileum with the cecum and in these cases there is ileal stasis beyond twenty-four hours, and very marked ileocecal valve incompetency—although the ileocecal valve incompetency by itself is no indication of disease. Very often bubbles of gas are encountered in the lower ileum likewise due to the ileocecal adhesions.

**Indirect Roentgenologic Signs.**—Indirect roentgenologic signs are much less reliable, but worthy of mention. They consist of unexplained ileal stasis due to spasm of the ileocecal valve, cecal stasis, spasticity or atony of the cecum, spasm of the pylorus and often spasm of the greater curvature of the stomach if pressure is exercised over the appendicular region under the fluoroscope.

### CONCLUSIONS

1 Attention has been directed to the differential diagnosis of gastric or duodenal ulcer and chronic appendicitis especially as it pertains to these diseases when the symptoms are extremely atypical.

2 Gastric or duodenal ulcer seldom causes symptoms referable to

the ileocecal region. On the other hand, the ileogastric syndrome, where the lesion is in the appendix or in the ileocecal region, does frequently simulate gastric or duodenal ulcer.

3 Hemorrhage occurring in cases of chronic appendicular disease is more resistant to medical treatment than hemorrhage due to peptic ulcer, and gives rise to a protracted anemia. Removal of the diseased appendix may permanently relieve the gastric symptoms.

4 Symptoms simulating gastric or duodenal ulcer, due to chronic appendicitis, have a greater tendency to persist throughout the entire year with very transient relief.

5 In cases of pylorospasm and duodenitis, if the diseased appendix is removed, it is essential to treat the patient postoperatively, both dietetically and emotionally for a long time, in order to prevent recurrence of gastric symptoms or the possibility of eventual ulcer formation.

6 In the differential diagnosis, in addition to the clinical symptoms, there must be careful roentgenologic study of the ileocecal region with particular emphasis on the appendicular region.

#### BIBLIOGRAPHY

- 1 Gaithes, Ernest H. Abdominal Syndromes of Exceptional Interest. *Southern M J*, Vol 25, No 10, Oct, 1932
- 2 Wolf, Stewart and Wolff, Harold G. *Human Gastric Function*. New York, Oxford University Press, 1943
- 3 Braithwaite, L R. *Brit J Surg*, 30 15, 1942
- 4 Gross, M H and Held, I W. Indications for Surgical Interference in Ulcus Ventriculi. *Surg, Gynec & Obst.*, Dec, 1918, pp 567-577
- 5 Held, I W and Goldbloom, A A. Roentgenologic Studies of the Mucous Membrane as an Aid in the Diagnosis of Peptic Ulcer. *Am J Roentgenol*, 26(1) 74 (July) 1931
- 6 Ratnoff, Oscar D and Patek, J, Jr. The Natural History of Laennec's Cirrhosis of the Liver. *Medicine*, 21 207 (Sept) 1942
- 7 Behrend, M. *Am J Surgery*, 63 90 (Jan) 1944
- 8 Held, I W. Chronic Appendicitis and Its Differential Diagnosis. *Am J M Sc*, 167(6) 864 (June) 1924

# DIVERTICULOSIS AND DIVERTICULITIS A CLINICAL STUDY OF THE COMPLICATIONS

KIRBY A. MARTIN, M.D., F.A.C.P.\* AND  
CHARLES G. ADST, JR., M.D.†

THE purpose of this clinic is to present some data on diverticulosis of the gastrointestinal tract and to comment on the complications and treatment of diverticula of the colon—diverticulitis, hemorrhage, perforation and intestinal obstruction

## LOCATION PREVALENCE AND AGE

Diverticula may be found in any part of the intestinal tract, only occasionally in the esophagus, stomach and small intestines, more frequently in the duodenum and very commonly in the colon, especially in its distal half. They may be congenital (Meckel's) but usually are acquired, if the latter, they are frequently multiple.

Diverticula have been known to the anatomists as a rare finding for centuries, but the first description of them as an entity was that of Sommering in 1794 and Chuvellier in 1849. Virchow in 1853 was the first to define them clinically. It was not until 1898, however, that a case of perforated diverticulitis with resulting left-sided peritonitis was reported by Graser. Lewald in 1914 is credited with the first roentgenologic diagnosis, but the prevalence of diverticula was not fully appreciated until the opaque motor meal x-ray technic became a common diagnostic procedure. Their importance as a clinical entity is still in a process of evolution.

X-ray and postmortem examinations of the intestinal tract have shown diverticula to be uncommon before the age of 35 and increasingly frequent after 45 years. The incidence is usually stated to be higher in the male than in the female, also more common in the obese. They are frequently seen proximal to a partial obstruction. Numerous authors have stated that they are found in about 5 per cent of persons subjected to x-ray examination for any cause.

Kocour<sup>1</sup> studied the incidence of diverticulosis in 7000 consecutive autopsies, and gives the percentage in each age decade. His figures show the condition to increase markedly in frequency after the age of 40, and to become relatively stationary after the sixtieth year. Of the patients over 40 years of age, 3.58 per cent showed diverticulosis.

---

From the Department of Medicine, Cornell University Medical College and the New York Hospital, New York City.

\* Instructor in Medicine, Cornell University Medical College. Assistant Attending Physician, New York Hospital.

† Assistant Attending Physician, Outpatient Department, St. Luke's Hospital.



and 0.15 per cent showed some complications which had caused the death of the patient. Contrary to most observations, his data show the incidence of diverticulosis in the female to be 33 per cent higher than in the male.

Diverticula, when once formed, persist. Only occasionally do they produce symptoms. The patient whose colon is x-rayed usually has some symptoms to justify the procedure and then the failure to show diverticula does not necessarily disprove their presence. They may fail to fill at times, as does an appendix. It would thus follow that consecutive autopsies in a large series, in which special attention was paid to this condition, would be more likely to represent the true incidence of the disease than conclusions based upon clinical findings. It is interesting that Kocour found the incidence of gallbladder disease in persons over 40 years of age to be double in those also having diverticulosis.

#### PATHOGENESIS

Anatomically, diverticula are blind sacs with small bases branching from the gastrointestinal tract. The pathogenesis is still incompletely understood. There is a common belief that the herniations occur at the point of entrance of a blood vessel into the wall of the bowel. To support this thesis, diverticula are frequently seen to develop in two parallel rows on either side of the mesocolon. Fansler<sup>2</sup> disagreed with this concept and stated that it is unusual to find a blood vessel adjacent to the neck of a diverticulum, especially in the colon. It is his opinion that diverticula develop in the haustrations or sacculations of the colon, in the wall of which only one layer of muscle (circular) is found. In these haustrations, the susceptibility of the muscular wall to stretching and thinning is increased, especially in the descending colon and sigmoid where the intestinal tension is greatest. This stretching and thinning in older individuals he believes may result in herniation and formation of diverticula. In agreement with this is the experience of not infrequently finding diverticula on any or all sides of the colon. The wall of the diverticulum is therefore formed from mucous, submucous and peritoneal coats, and at times acquires a fatty coat.

#### DIVERTICULITIS

Diverticulosis which precedes diverticulitis is present, as previously stated, in about 5 per cent of persons subjected to x-ray examination of the colon for any cause. Diverticulitis develops in about 12 to 15 per cent, according to Graham.<sup>3</sup> In other words, diverticula cause no symptoms in most instances. They are, however, potential sources of danger in producing localized stasis, inflammation and ulceration of the sac, with possible perforation. The sigmoid and descending colon are the most common areas to meet with these complications.

## DIVERTICULA OF THE SIGMOID AND DESCENDING COLON

Further discussion in this clinic will be limited to the consideration of symptoms, diagnosis and treatment in the complications of diverticulosis found in the sigmoid and descending colon. The statistical data to be presented were obtained by reviewing the material in the record room of the New York Hospital. The selected case records were taken from our private files. The opinions expressed obviously are wider than the analysis of the material would permit.

TABLE 1—DATA CONCERNING DIVERTICULITIS AT NEW YORK HOSPITAL,  
1933 TO 1944\*

Total admissions to New York Hospital	177 718
Cases of diverticulitis	201
Percentage of admission	0.001
Sex	105 males, 96 females
Duration of symptoms	2 hours to 54 years
Associated with	
Carcinoma of large bowel	
Other carcinoma	
Cholecystitis and cholelithiasis	
Gastric ulcer	
Duodenal ulcer	
Constipation	
Diarrhea	
Constipation and diarrhea	
Hemorrhage†	
Perforation	
Fistula	
Perirectal abscesses	
Confused with	
Carcinoma of sigmoid	
Appendicitis	
Renal colic	
Deaths	
Perforation	
Hemorrhage	
Other	
Cases of Meckel's diverticulum	
Females	
Males	

TABLE 2 —SITE OF THE DIVERTICULA, ACCORDING TO AGE

Age	Diverticula		Total
	Meckel's	Colon	
0 - 10	17		17
11 - 20	4		4
21 - 30	2	1	3
31 - 40	3	12	15
41 - 50	2	24	26
51 - 60		54	54
61 - 70		58	58
71 -		24	24

TABLE 3 —MECKEL'S DIVERTICULUM AT THE NEW YORK HOSPITAL OVER  
TWELVE YEARS  
(Total Admissions 177,718)

	No	Per Cent
Total cases	28	
Total deaths	2*	7.14
Cases operated on	14	50.00
Postoperative deaths	0	0

\* One stillborn, one newborn, no operations

TABLE 4 —DIVERTICULITIS REQUIRING OPERATION

	No	Per Cent
Total cases operated on	51	
Perforation	25	49.0
Hemorrhage	17	33.3
Diverticulosis and carcinoma	4	7.8
Deaths	12	23.5
Deaths excluding carcinoma	9	17.6
Cases explored for possible carcinoma	13	25.5
Carcinoma found	4	7.8
Deaths from carcinoma	3	5.9
Deaths excluding carcinoma	0	0

### SYMPTOMS AND DIAGNOSIS

The symptoms vary greatly, from a single slight acute attack, recurring episodes or chronic inflammatory reaction, to acute or chronic perforation with localized peritonitis and abscess formation or general peritonitis. A fistula occasionally develops between the sigmoid and the vagina or the urinary bladder, the latter manifesting itself by the urine containing gas and fecal material.

Local manifestations, if present, are usually in the left lower quad-

rant of the abdomen, but may be in the midline or to the right side, depending upon the position of the sigmoid and its tension, a spastic sigmoid may produce back pressure in the cecum and appendix, and the latter may be blamed for the symptoms. Pain on pressure over the sigmoid, muscle guard, spasm and flatulence are common. The symptoms usually give little information as to the extent of the lesion unless a tumor mass is felt.

In other instances a dull intermittent or constant cramplike diffuse pain in the abdomen frequently associated with tenesmus is common, or the symptoms may be entirely rectal. A significant sign is the temporary relief that may follow a warm saline enema, a bowel movement or the passing of flatus. Fever and leukocytosis may be present. Diarrhea and constipation are equally common. Rectal bleeding does occur, but is rare except in Meckel's diverticulum, it may follow the passing of diverticular concretions, but blood in the stool indicates carcinoma until disproved.

The clinical picture associated with diverticulitis can simulate almost any other abdominal disease. The importance of making a proper diagnosis is therefore obvious, operation is rarely advised in diverticulitis. Furthermore, the postoperative mortality was 20 per cent, with a residual mortality of 29 per cent in Babcock's<sup>4</sup> series. In our series it was 23.5 per cent. X-ray study is indispensable in this work and if used to its fullest extent, fruitless surgical procedures can be avoided.

#### DIFFERENTIAL DIAGNOSIS

In most cases it is easy to distinguish carcinoma from diverticulitis, difficult in a few, and almost impossible in an occasional case. In this latter group exploratory laparotomy may be necessary. The operator frequently encounters a hard, irregular, fixed mass involving the sigmoid or descending colon and the diagnosis may remain uncertain pending the microscopic study. Carcinoma, like diverticulosis, is most commonly found in the sigmoid and descending colon, although the association of the two is so rare that there is no reason to believe that diverticulosis is a precursor of cancer.

*Proctoscopic examination* is indicated. It is not uncommon to find a carcinoma of the rectum producing the symptoms, although the radiographs may be negative save for the presence of diverticula or perhaps diverticulitis of the sigmoid.

Blood, pus and excess mucus with a foul odor coming from some point higher than the rectum usually means carcinoma, but occasionally an intramural abscess in peridiverticulitis will give a similar picture if the abscess is draining into the gut. In all such cases a complete gastrointestinal study is indicated.

*Radiographic study* is a valuable adjunct in the diagnosis of diverticulitis, in most cases it is all that is necessary. In complicated cases, however, the responsibility for the differential diagnosis is great. Still

the balance of evidence is in the interpretation of the radiographic findings, but the clinician who marshals all the clinical data in a given case will err less frequently

In acute uncomplicated cases the inflamed, edematous walls present a bizarre sawtooth outline giving such a characteristic radiograph, during a barium enema, that it is not likely to be confused, even though no diverticula are seen (Case III) But diagnosis is more difficult in acute exacerbation of a chronic diverticulitis, a subacute or chronic peridiverticulitis which has produced a thick wall and a constricted lumen of the gut with cone-shaped ends (Case VII, *A*) There is usually a distortion of the pattern of the mucosal folds and a marked deformity of the bowel lumen (Case V) Air contrast enema and spot films of mucosal pattern are usually helpful in such cases Still more complicated are those that develop intramural abscesses, losing part of the mucosal pattern (Case VII, *B*) Diverticula with long necks are common in such cases, and if they should fall at either end of the constriction, they may produce an overhanging edge like that seen in carcinoma The two conditions do coexist occasionally and the presence of diverticula proximal or distal to the constricted area does not exclude carcinoma, as illustrated in Case IX

The presence of diverticula does not help much in the differential diagnosis, but their absence does if proper delayed x-ray films are made following an opaque motor meal However, the presence of diverticula in the constricting mass is important because they rarely if ever occur in carcinoma (Schatzki<sup>6</sup>) (Case VIII)

#### TREATMENT

The treatment is medical in all but those few cases in which serious complications may or do occur The predominant symptom in the average uncomplicated case is *spasm* of smooth muscle, the result of inflammation in the diverticula The duration or intensity of the symptoms is such that only an occasional patient consults his physician In more severe cases the following treatment is usually effective Rest in bed, heat to abdomen, smooth diet, sedative, antispasmodic and inducing bowel movement with the least possible irritation Phenobarbital gm 0.032 ( $\frac{1}{2}$  grain), three times a day, or tincture of belladonna 1.9 cc (30 drops) single or combined (we have never been impressed with the virtues of the latter) Mineral oil is beneficial during the acute phases, at the expense of a possible avitaminosis Codeine 0.06 gm (1 grain) or paregoric 4 cc (1 dram) may be indicated Warm saline or oil enemas usually give comfort Barium sulfate in 28.4-gm (1 ounce) doses, given in a water suspension two or three times a week is beneficial The barium supposedly displaces the irritating, fermenting intestinal content, reducing the inflammation and edema The improvement of symptoms that so frequently follows x-ray study of the colon amply confirms this statement

*Obstruction* develops slowly as a rule, and is rarely complete. It may be the first symptom. The treatment is secondary to the diverticulitis. We encountered this only eight times in our series.

*Acute perforation* has been rare in our experience. It has been stated to occur about one half as often as perforation from carcinoma. We had eight cases. Acute perforation from a diverticulum in the colon, like acute perforation from any cause, calls for immediate operative closure. These patients usually do well.



Fig. 125—(Case I.)

*Slow perforation* Perforation from a diverticulum or an intramural abscess is more common than acute perforation and, unlike an appendix, is likely to produce few symptoms for long periods of time, due to a slow but complete walling-off process.

The sulfonamides have not been impressive, in our experience, in the uncomplicated cases or in those that perforate and form abscesses or fistulous tracts. Likewise in our limited experience, penicillin was beneficial only in secondary complications (Case VII, B).

This group likewise is managed surgically. The exploratory laparotomy, as well as the postmortem findings, in these cases usually

shows a widespread mesentery and lymph gland inflammatory involvement. This, in addition to abscess and sinus tracts, makes resection of the affected segment of the gut a hazardous task.

### CASE REPORTS

#### CASE I

*Clinical* Woman, 53. Loss of 15 pounds of weight. No intestinal symptoms.

Normal bowel function.

*Film* (Fig 125) 24-hour barium motor meal.

*Diagnosis* Diverticulosis of colon.

*Accessory* Osteogenesis imperfecta, has had fourteen fractures.



Fig 126 — (Case II)

#### CASE II

*Clinical* Man, 55. Vague abdominal distress for ten years, worse in past three months.

*Film* (Fig 126) 24-hour barium motor meal. In transverse colon note "pseudo-diverticula." Barium enema films showed no evidence of organic disease.

*Diagnosis* Duodenal ulcer, right renal calculi. Spastic colon.

#### CASE III

*Clinical* Man, 51. Acute abdominal pain, typical "left side appendicitis." Six years later, no further symptoms.

*Film* (Fig 127) Barium enema (film reversed). Note spasm in sigmoid, spikes set at varying angles to the lumen. No diverticula seen in sigmoid, one noted in transverse colon. On delayed films two small diverticula were seen in sigmoid.

*Remarks* Typical of acute, early diverticulitis.

## CASE IV

*Clinical* Man, 51 No intestinal symptoms until ten hours before. Onset with acute left lower abdominal distress and a sudden desire to defecate and pass flatus. Diarrhea lasted three hours, followed by frequent periods of straining and tenesmus but passing only small amounts of mucus and bright red blood.

*Proctoscopic* From some point above the rectosigmoid area mucus and bright red blood came into view otherwise the examination was negative.



Fig 127—(Case III.)

*Film* (Fig 128) Barium enema. Note spasm in sigmoid with spikes set at various angles to the bowel lumen. (Postevacuant film showed four small diverticula.)

*Diagnosis* Acute diverticulitis of sigmoid with hemorrhage

*Result* Symptoms subsided

## CASE V

*Clinical* Man, 55 Many attacks of left lower abdominal distress none in acute phase, until now

*Film* (Fig 129) Postevacuation barium enema, plus air injection. Note spiral stair" effect from deep folds of mucosa. Diverticula are at apices of these folds.

*Diagnosis* Acute phase of chronic diverticulitis.





Fig 128 —(Case IV)



Fig 129 —(Case V)

**CASE VI, A**

*Clinical* Man, 55 Generally constipated During past ten years repeated attacks of diarrhea and lower abdominal distress Now, temperature 100° F, pulse

95, white blood cells 11,000 pain in left lower quadrant. Desire to defecate and pass flatus slight muscle guard Palpable mass in left lower quadrant.



A



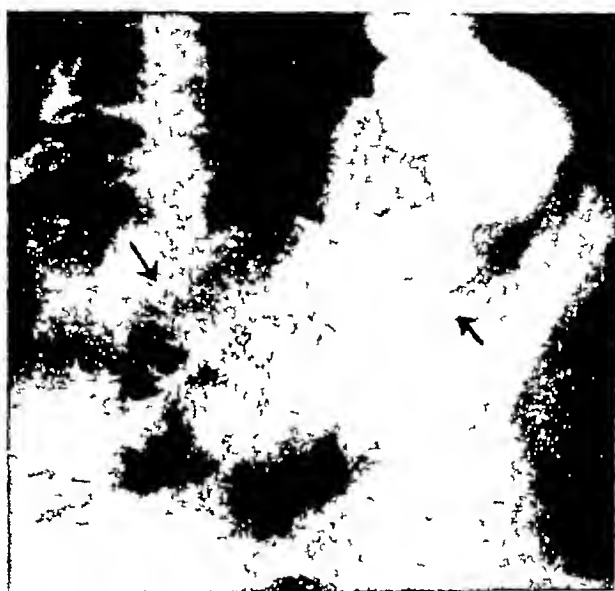
B

Fig 130—(Case VI)

*Film (Fig 130 A) Barium enema. Narrowing of the sigmoid lumen with a symmetrical arrangement of diverticula with long necks, "accordion type"*  
*Diagnosis Acute exacerbation of a chronic diverticulitis, peridiverticulitis.*

## CASE VI, B

Same case four years later, following operation for acute perforation at the proximal end of narrowing Patient had been asymptomatic for nine months



A



B

Fig 131 — (Case VII)

*Film* (Fig 130, B) Barium enema Funnel-shaped shadows at base of some diverticula, probably fecalith

*Comment* Prognosis is poor, resection advised

## CASE VII A

*Clinical* Woman 63 Constipated treated fifteen years for "colitis" First symptom was acute, severe rectal pain Temperature 104 F., pulse 140 white blood cells 18 000 No abdominal signs or symptoms. Rectal and vaginal examination negative save for general discomfort. Later stool contained blood and pus

*Film* (Fig 131 A) Barium enema. Filling defect in sigmoid colon much spasm partial intestinal obstruction. Note numerous diverticula with long necks at unusual distances from the central axis of the gut.

*Diagnosis* Diverticulitis, acute phase of a chronic peridiverticulitis, intramural abscess and question of perforation of a diverticulum with pelvic abscess partial obstruction of colon.

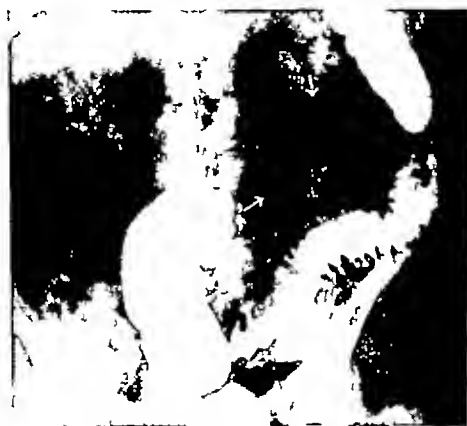


Fig 132 —(Case VIII)

## CASE VII B

In same case two days later a sigmoid vaginal fistula developed Temperature subsided and general condition improved until a four year old osteomyelitis of leg became active Sulfonamides had no apparent effect on abscess or osteomyelitis One million units of penicillin effected a quick subsidence of the osteomyelitis but had no demonstrable effect on the pelvic abscess.

*Film* (Fig 131 B) 36-hour barium motor meal plus barium enema. Note evidence of intramural abscesses and a fistulous tract to pelvic abscess indicated by arrows

*Outcome* Resection of sigmoid colon three months following a colostomy Patient died thirty-six days postoperatively of general peritonitis and sepsis.

*Surgical Pathology* Specimen removed at operation showed an 18-inch segment of colon 12 inches of which were dense, firm and greatly thickened with many diverticula, intramural abscesses and intramural fistulas, some communicating with the lumen of the bowel and one to the external surface

## CASE VIII (Courtesy of Dr Frederic Bancroft)

*Clinical* Woman, 80 Intermittent attacks of left lower quadrant pain for forty years Lost 15 pounds in last seven months, abdominal distress worse. Diarrhea, with blood in stool Palpable mass in left lower quadrant.

*Film* (Fig 132) Fixed irregularity in outline of descending colon with eccentric lumen Mucosal pattern destroyed No diverticula seen in area of filling defect but are numerous distal to same Note large soft tissue shadow indicated by arrows Probably a cyst, had no relation to colon, was not explored

*Diagnosis* Carcinoma of colon with partial colonic obstruction Diverticulitis chronic type

*Operation* Resection of descending colon and sigmoid-anastomosis, colostomy closed

*Pathology* Diagnosis—adenocarcinoma of colon, peridiverticulitis of colon

*Result* Discharged home—bowel function normal



Fig 133 —(Case IX.)

## CASE IX

*Clinical* Man, 53 Moderate constipation for several years, with many attacks of vague abdominal distress Since past ten months has had tendency toward diarrhea, more recently has had blood in stool, no weight change

*Film* (Fig 133) 36-hour motor meal, plus barium enema Large constant filling defect in descending colon with partial colonic obstruction Note numerous diverticula with long necks on medial side of filling defect and no diverticula lateral side, save one at upper border producing an overhanging edge, mucosal pattern destroyed

*Diagnosis* Diverticulitis, peridiverticulitis of descending colon and sigmoid with colonic obstruction, question of carcinoma of descending colon

*Operation* Resection and end-to-end anastomosis Specimen showed a chronic peridiverticulitis with an ulcerating carcinoma on lateral wall

*Result* Recovered

## COMMENT

In practice many cases of colonic disturbance are labeled and treated as "colitis" without proper examination and study. Most will prove to be functional, but an occasional one will have an organic lesion responsible for the symptoms. A significant point to suggest the latter is *a change in the bowel rhythm, a change in the rate of flow* (diarrhea or constipation) or *a change in character of the content* (increase or decrease of fluid, presence of blood, mucus or pus). Diagnosis is the first consideration.

It is to be borne in mind that this study, for the most part, represents only the occasional case of diverticulitis in which the patient was sufficiently ill to be admitted to the hospital. The disease is very commonly met in ambulatory practice and rather infrequently in hospital practice.

The severity of the symptoms gave no clue in most instances as to the stage of the disease process. This fact has a tendency to lessen the percentage of severe complications to the total group. And, for the same reason, a large percentage responded well to medical treatment.

Acute perforations, when they did occur, were frequently found in the absence of other complications, such as peridiverticulitis, and if recognized early, usually did well following operative closure of the perforation.

In the group in which peridiverticulitis was the predominant feature, partial colonic obstruction, slow perforation with abscess formation and fistula were common complications. Our data support the view that there has been no significant change in the mortality rate in this group in twenty-five years, despite the general progress in medical management in many other conditions. Peridiverticulitis and carcinoma are most commonly found in the descending and sigmoid colon. They also have in common the same age group. The treatment of diverticulitis is generally considered medical, carcinoma surgical. In several instances a preoperative positive diagnosis was impossible and a resection of the lesion was carried out. In Table 4 you will note that there were thirteen operations on such cases and only four carcinomas were found. If we exclude these four carcinomas the mortality drops to 0 against 22.9 in the group as a whole. The difference lies in the fact that infection as a complication was infrequent. The fault, therefore, would appear to lie in the continued failure to recognize those cases with impending danger as a separate group and institute proper surgical measures. This is a serious criticism of our diagnostic acumen, but improvement will follow if operation is offered early as a preventive of a too-often widespread infection and fatal outcome.

## SUMMARY

During the period between 1933 and 1944 there were 201 patients with acute diverticulitis admitted to the New York Hospital in a total admission of 177,718 patients, or 0.00112 per cent

There were 28 cases of Meckel's diverticulum, or 0.00016 per cent. Fourteen patients were operated on with no postoperative deaths

There were 51 cases operated on for some complication in relation to the diverticulitis with 12 deaths, or 23.5 per cent

Carcinoma was encountered in the presence of diverticulitis in 4 cases, or 7.8 per cent

Carcinoma was suspected and operation carried out on 13 cases (25.5 per cent), with 3 deaths, or 5.9 per cent. Excluding carcinoma, it was 0 against 23.5 per cent in the group as a whole

Peridiverticulitis, like carcinoma, occurs in the same age group and is most commonly found in the descending and sigmoid colon. The lesion formed is frequently confused with carcinoma and may lead to serious complications, followed by a high mortality rate. Data are presented to suggest how a differential diagnosis can be made and how the mortality rate can be lowered

## BIBLIOGRAPHY

- 1 Kocour, E. J. *Am J Surg*, 37:433, 1937
- 2 Fansler, W. A. *Tr Am Proctolog Soc*, 41:231, 1940
- 3 Graham, R. R. *Canad M A J*, 36:1 (Jan) 1937
- 4 Babcock, W. W. *Rev Gastroenterol*, 8:72, 1941
- 5 Schatzki, R. *Radiol*, 34:651, 1940

## TREATMENT OF CIRRHOSIS OF THE LIVER BY NUTRITIONAL MEANS

NORMAN JOLLIFFE, M D \* AND ELMER ALPERT, M D †

### NUTRITIONAL DEFICIENCIES AS BASIS OF CIRRHOSIS OF LIVER

THE basic difficulty in formulating an effective treatment for cirrhosis of the liver has been our ignorance of the pathogenesis of this disease. In the past decade, however, some evidence has been presented showing that cirrhosis of the liver may have its pathogenesis in some form of malnutrition Jolliffe and Jellenik,<sup>1</sup> after reviewing the literature, point out that the weight of scientific evidence dismisses the direct causation of cirrhosis by alcohol

Cirrhosis of the liver has been produced experimentally by dietary means The lack of certain factors contained in yeast<sup>2 3 4</sup> or casein<sup>5 6 7 8 9</sup> brings about fibrotic changes in the livers of rats and rabbits Fatty infiltration and cirrhosis have been produced by diets low in protein and high in fat.<sup>4 7 8, 10</sup> Low protein, choline-poor diets produce cirrhosis of the liver in rats which is characterized by fatty infiltration and the appearance of a hyaline substance in the liver cells<sup>6</sup> Addition of choline, a high casein diet or choline with a high casein diet produced regression of the fatty changes and regeneration of liver cells<sup>11</sup> The feeding of excess cystine<sup>12</sup> also is said to produce liver cirrhosis in experimental animals Halliday<sup>13</sup> was able to demonstrate an increased liver lipid content in rats deficient in vitamin B<sub>6</sub> as compared with normal animals Fouts<sup>6</sup> produced a deficiency state in dogs in which fatty cirrhotic livers occurred on a low protein diet supplemented with thiamine, riboflavin, nicotinic acid, pyridoxine and a pantothenic acid which could be improved by the administration of liver extract.

Nutritional deficiencies as a basis of cirrhosis of the liver were suggested even before vitamin deficiencies had received consideration Klieneberger<sup>14</sup> attributed the severe forms of cirrhosis to poor nutrition in 1923, and ten years later, Kennedy<sup>15</sup> suggested that alcohol acted more as a factor contributing to dietary deficiency than as a toxic substance Connor<sup>16</sup> reporting the results of his classical experiments on dogs, stated, "There can be little doubt now that alcohol and the habits induced by the consumption of large amounts of alcohol

---

Associate Professor of Medicine, New York University College of Medicine, New York City Formerly Chief of the Medical Service of the Psychiatric Division of Bellevue Hospital

† Passed Assistant Surgeon (R) United States Public Health Service. Formerly Resident Physician, Medical Service, Psychiatric Division, Bellevue Hospital



are the most important factors concerned with the production of fatty liver which passes on in some cases to cirrhosis "

Alcoholic patients with cirrhosis often have been on deficient diets for long periods of time, and the incidence of certain deficiency states in liver cirrhosis is not small. Peripheral neuropathy<sup>17</sup> and signs of niacin deficiency<sup>18</sup> occur in a high percentage of cases of cirrhosis. Patek<sup>19</sup> found polyneuritis in 40 per cent and a smooth tongue in 60 per cent of fifty-four patients with cirrhosis of the liver. The cirrhotic often enters the hospital exhibiting one of the types of alcoholic encephalopathy for which an avitaminotic etiology has been postulated.<sup>20 21</sup> In 200 cases of cirrhosis of the liver on the Medical Service of the Psychiatric Division, Bellevue Hospital, 20 per cent of the patients were in the encephalopathic state on admission, including Wernicke's syndrome, nicotinic acid deficiency encephalopathy, the Korsakoff psychosis and nonspecific alcoholic encephalopathies. Not alone the vitamin B complex but also a deficiency of vitamin K is found concomitant with the cirrhotic state. A lowered prothrombin level in cirrhosis has been found by several groups of investigators.<sup>22 23 24</sup> This is due to the fact that the liver is responsible for the utilization of vitamin K in the synthesis of prothrombin.

Other manifestations of the cirrhotic syndrome emphasize its nutritional relationship. The presence of ascites is one of the most important determining factors in prognosis and is usually, but not always, associated with demonstrable changes in the serum proteins. The total proteins are reduced, or if normal, the albumin fraction is decreased with a compensatory increase in globulin, resulting in an inversion of the albumin-globulin ratio. Since Starling<sup>25</sup> pointed out the role of the serum protein in the maintenance of the colloid osmotic pressure of the blood, several workers<sup>26 27</sup> have shown a correlation between the reduced level of serum albumin and the accumulation of ascites. Post and Patek,<sup>28</sup> from a study of the serum proteins in cirrhosis of the liver found that the changes in level of the serum albumin have a good correlation with the clinical course. In those patients whose course is unfavorable, the serum albumin either remains low or declines.

Recently, a definite relationship has been pointed out between vitamin B and serum proteins in edema. Field<sup>29</sup> observed cases with edema and lowered plasma protein despite diets apparently adequate in both proteins and vitamins. Relief followed supplementation with vitamin B complex. These include cases of cirrhosis of the liver, in one of which the patient has been maintained edema-free and with nearly normal serum protein despite increasing impairment of liver function.

Anemia may be present in from 40 to 90 per cent<sup>18 30, 31</sup> of the patients with cirrhosis of the liver. It is frequently of the hyperchromic, macrocytic types found in pernicious anemia. This finding is probably due to the inability of the damaged liver to store the anti-anemic factor.

Cirrhosis of the liver may occur in association with many factors which act as hepatotoxic substances, such as chemical poisons, syphilis, a variety of systemic diseases, hyperthyroidism, toxemia of pregnancy and toxins of intestinal origin. The experimental studies demonstrate that it is difficult to produce permanent and severe parenchymatous liver disease except when the liver is in an abnormal state. It may well be that the factor common to the action of all hepatotoxic substances in the production of cirrhosis is in some altered chemical state caused by the poor nutrition of the liver. It might be well, therefore, to mention briefly some of the more important factors which can protect the liver from the adverse action of numerous toxins.

Studies on experimental animals have demonstrated the lipotropic action of several factors, i.e., substances which prevent the deposition of fat in, or accelerate its disappearance from the liver. Large fatty livers were found in depancreatized dogs maintained on a mixed diet and insulin, which could be prevented by the addition of fresh beef pancreas. Hershey and Soskins<sup>32</sup> found that lecithin contained the same lipotropic activity and it was then demonstrated that choline was the active component of this phospholipid.<sup>33, 34</sup> Subsequently the lipotropic activity of choline, when added to diets of rats in whom cirrhosis had been produced, was shown by several investigators.<sup>11, 35, 36, 37</sup>

The first evidence that protein affected the deposition of fat in the liver was obtained by Best and Huntsman.<sup>36</sup> They found that the addition of casein to a deficient diet reduced the amount of fat in the liver. It was thought that the lipotropic action of casein was not due to the negligible amount of choline it contained. It was suggested that its action might be through the methionine which possesses labile methyl groups which may be the determining factor in lipotropic activity.<sup>37</sup>

Elman and Heifetz<sup>38</sup> have demonstrated definite impairment of the liver function in protein depleted animals, and conversely, it has been shown that dietary protein may protect the liver against the effects of exogenous toxins.<sup>39, 40, 41</sup> Fagin, Sahyun and Pagel<sup>42</sup> analyzed the liver specimens from alcoholic patients with cirrhosis of the liver for their total lipid and nitrogen content. They found that specimens from patients who had received a fortified casein hydrolysate as part of their therapy contained a greater percentage of protein and a lesser percentage of fat than specimens from patients who had not received casein hydrolysate.

#### DIETARY TREATMENT

Patek<sup>19</sup> and Patek and Post<sup>43</sup> reported on a series of fifty-four patients with cirrhosis of the liver who were given a diet rich in protein and ample in carbohydrate and fat. The diet contained protein 139 gm., fat 175 gm. and carbohydrate 365 gm., furnishing 3591 calories. The diet consisted chiefly of meat, milk, eggs, fruit and green vege-

tables, and was supplemented with 50 gm of brewers' yeast daily. In addition, thiamine hydrochloride 5 mg was injected daily and liver extract 5 cc twice weekly. Of the fifty-four patients on this regimen, twenty-two showed signs of progressive failure, twelve made partial improvement, and the remainder showed signs of "clinical recovery."

In comparison with a control group, the period of survival of these patients showed the following differences. At six months, 57 per cent of the controls were alive in contrast to 72 per cent of the treated series, at one year 39 per cent of the controls and 57 per cent of the treated series, at two years 22 per cent of the controls and 45 per cent of the treated series. In addition to the increased period of survival there were signs of general bodily improvement, disappearance of ascites, edema, jaundice and vascular spiders, together with improvement in certain laboratory tests.

Fleming and Snell<sup>44</sup> also reported significant clinical improvement in 44 per cent of a group of patients receiving a high protein, high carbohydrate diet supplemented with large doses of vitamins, as compared with satisfactory results in 31 per cent of patients receiving a high carbohydrate diet and diuretic agents.

#### USE OF LIPOTROPIC FACTORS

Broun and Muether<sup>45</sup> reported a good response by patients with hepatic cirrhosis to the administration of choline chloride, 1 gm daily plus a low fat, high protein diet. On the other hand, Yater<sup>46</sup> in a study of fifteen patients, does not think that choline is effective in treatment of cirrhosis. In addition to a high protein, high carbohydrate, low fat and high vitamin diet (protein 215 to 150 gm, fat 50 to 60 gm, carbohydrate 300 gm) Russakoff and Blumberg<sup>47</sup> administered choline chloride orally in doses of 2 gm three times daily. Seven of the nine patients so treated showed definite clinical improvement with reduction in the size of the liver, great diminution or disappearance of ascites, increase in the serum albumin, improvement of the hemogram, decrease of the prothrombin time and normal liver function tests. Two patients, one with an enlarged fibrotic but nonfatty liver and one with a small shrunken liver, failed to improve. In a series of unreported cases at Bellevue Hospital, the administration of raw pancreas, and large doses of casein and choline either alone or in combination, failed to influence the course of the hepatic cirrhosis. However, the poor results may well have been due to the short period of treatment of these patients.

Beattie and Marshall<sup>48</sup> obtained considerable success in preventing and treating liver damage due to widely differing causes by the administration of methionine or by the use of casein digests with the methionine.

## GENERAL COMMENT

The nutritional treatment of cirrhosis of the liver implies intelligent, patient nursing care. Most cirrhotics have poor appetites and an aversion for food, making the consumption of a full diet a real problem. The presence of ascites increases discomfort and adds to the difficulty of eating because of mechanical interference with the gastrointestinal tract. For this reason it may be advisable to reduce the amount of ascitic fluid present, either by diuretics or by abdominal paracentesis.

On the Medical Service of the Psychiatric Division of Bellevue Hospital,<sup>40</sup> it was found that the cause of death of patients with cirrhosis of the liver, who succumbed within the first ten days after admission, was, as a rule, not due to progressive liver failure per se, but rather either to infection or to one of the encephalopathic states. Jolliffe and Wortis<sup>21</sup> have pointed out the probable avitaminotic etiology of these syndromes. It may be necessary, therefore, to institute immediate parenteral vitamin therapy in large doses to prevent rapid death in the encephalopathic state, before caring for the underlying cirrhosis. Specifically the diet should be high caloric, high vitamin and high protein. With patient effort many patients with cirrhosis can be coaxed to eat 140 gm of protein, though in many patients, 100 gm seems to represent the upper limit of tolerance.

In addition to the large amounts of protein in the diet, we have been impressed recently with the seemingly better results obtained by supplementing the diet with large amounts of a fortified casein hydrolysate so that the nitrogen intake is made to approach 0.6 gm of nitrogen per kilogram of body weight. This diet then should be supplemented by a source of the natural B-complex such as brewers' yeast or its extracts. If this causes too much stress on the gastrointestinal tract we administer a crude liver extract (5 cc) by intramuscular injection. For vitamin supplementation we have preferred a formula containing thiamine 10 mg, riboflavin 5 mg, niacinamide 50 mg., and ascorbic acid 100 mg. In addition vitamin A in 50,000 units twice daily is given and, when indicated, one of the preparations of vitamin K. On this basic nutritional therapy of the cirrhotic, other therapy is instituted.

## SUMMARY

1 On the basis of experimental and clinical evidence, it is possible to postulate that the liver made more vulnerable by an unfavorable nutritional environment, reacts to a variety of toxins causing parenchymal damage by the deposition of excess amounts of neutral fat which may go on to progressive fibrosis and atrophy.

2 Favorable results in treatment have been obtained by the use of a high protein high carbohydrate, moderate to low fat diet, plus fortified casein hydrolysate, dried brewers' yeast by mouth, liver extract parenterally and administration of specific vitamins when indicated.

3 The lipotropic factors—casein, choline and methionine—either alone or in combination, may be used experimentally

## BIBLIOGRAPHY

- 1 Jolliffe, N and Jellinek, E M Vitamin Deficiencies and Liver Cirrhosis in Alcoholism Part VII Cirrhosis of the Liver Quart J Studies on Alcohol 2 544, 1941
- 2 Post, J., Earle, D P, Patek, A J and Victor, J Effect of Yeast and Food Intake on Experimental Carbon Tetrachloride Cirrhosis in the Rat Am J Path., 18 661, 1942
- 3 Rich, A R and Hamilton, J D The Experimental Production of Cirrhosis of the Liver by Means of a Deficient Diet Bull Johns Hopkins Hosp., 66 185, 1940
- 4 Webster, G T Cirrhosis Among Rats Receiving Diets Poor in Protein and Rich in Fat J Clin Investigation, 21 385, 1942
- 5 Daft, F S, Sebrell, W H and Lillie, R D Production and Apparent Prevention of Dietary Cirrhosis in Rats by Choline, Methionine and Casein Proc Soc Exp Biol & Med., 48 228, 1941
- 6 Lowry, J V., Daft, F S, Sebrell, W H, Ashburn, L L and Lillie, R D Treatment of Dietary Cirrhosis in Rats with Choline and Casein Pub Health Rep., 56 2216, 1941
- 7 Blumberg, H and McCollum, E V The Prevention by Choline of Liver Cirrhosis in Rats on High Fat, Low Protein Diets Science, 93 5981, 1941
- 8 Gyorgy, P and Goldblatt, H Observations on the Conditions of Dietary Hepatic Injury (Necrosis, Cirrhosis) in Rats J Exper Med., 75 355, 1942
- 9 Fouts, P J Vitamin B-Complex Studies in Dogs Production of Cirrhosis of Liver J Nutrition 25 217, 1943
- 10 Blumberg, H and Grady, H G Production of Cirrhosis in Rats by Feeding Low Protein, High Fat Diets Arch Path., 34 1035, 1942
- 11 Lillie, R D, Ashburn, L L, Sebrell, W H, Daft, F S and Lowry, J V Histogenesis and Repair of Cirrhosis in Rats Produced on Low Protein Diets and Preventable with Choline Pub Health Rep., 57 502, 1942
- 12 Channon, H J, Mamfold, M C and Platt, A P The Action of Sulphur-containing Amino-Acids and Proteins on Liver Fat Deposition Biochem J, 34 866, 1940
- 13 Halliday, N Fatty Livers in Vitamin B<sub>6</sub> Deficient Rats J Nutrition, 16 285, 1938
- 14 Klieneberger, Carl Typhus abdominalis und Lebercirrhose Zentralbl. f inn Med., 44 129, 1923
- 15 Kennedy, J A Psychosis with Alcoholic Pellagra Med Bull Veterans' Administration, 10 155, 1933
- 16 Connor, C L The Etiology and Pathogenesis of Alcoholic Cirrhosis of the Liver J.A.M.A., 112 387, 1939
- 17 Wayburn, E and Guerard, C Relation Between Multiple Peripheral Neuropathy and Cirrhosis of the Liver Arch Int Med, 66 161, 1940
- 18 Bean, W B, Spies, T D and Blankenhorn, M A Secondary Pellagra Medicine, 23 1, 1944
- 19 Patek, A J, Jr Dietary Treatment of Laennec's Cirrhosis with Special Reference to Early Stages of the Disease Bull New York Acad Med, 19 498, 1943
- 20 Jolliffe, N, Wortis, H and Stein, M H Vitamin Deficiencies and Liver Cirrhosis in Alcoholism Part IV The Wernicke Syndrome Part V Nicotinic Acid Deficiency Encephalopathy Part VI Encephalopathies

with Possible Nutritional Involvements *Quart. J Studies on Alcohol*, 273, 1941

- 21 Jolliffe, N and Worts H Encephalopathia Alcoholica An Evaluation of Vitamin Therapy *Am J Psychiat.* 98 340, 1941
- 22 Kaller T Das Vitamin K und seine klinische Bedeutung Thieme Leipzig 1941
- 23 Pahle F J and Steward J K. Observations on the Plasma Prothrombin and the Effects of Vitamin K in Patients with Liver or Biliary Tract Disease *J Clin Investigation*, 19 365 1940.
- 24 Scanlon G H., Brinkhaus, K. M., Warner E. D., Smith, H P and Flynn, J E. Plasma Prothrombin and the Bleeding Tendency with Special Reference to Jaundiced Patients and Vitamin K Therapy *J.A.M.A.*, 112 1898 1939
- 25 Starling E. H. On the Absorption of Fluids from the Connective Tissue Spaces. *J Physiol.*, 19 312, 1895
- 26 Myers, W K. and Keefer C. S. Relation of Plasma Proteins to Ascites and Edema in Cirrhosis of the Liver *Arch Int. Med.*, 55 349 1935
- 27 Butt H R., Snell A M and Keys, A.. Plasma Proteins in Hepatic Disease A Study of the Colloid Osmotic Pressure of Blood Serum and of Ascitic Fluid in Various Diseases of the Liver *Arch. Int. Med.*, 63 143 1939
- 28 Post, J and Patek, A. J. Serum Proteins in Relation to Liver Disorders. *Bull. New York Acad. Med.*, 19-815 1943
- 29 Field H The Relation of Vitamin B to Serum Proteins and to Edema *J Clin Investigations*, 16-663 1937
- 30 Wintrobe M M Relation of Disease of the Liver to Anemia Type of Anemia, Response to Treatment and Relation of Type of Anemia to Histopathologic Changes in Liver, Spleen and Bone Marrow *Arch Int. Med.*, 57 289 1936.
- 31 Rosenberg D H and Walters, A. Macrocytic Anemia in Liver Disease, Particularly Cirrhosis Observations on the Incidence, Course and Reticulocytosis with a Correlated Study of the Gastric Acidity *Am J M Sc.*, 192-86, 1936.
- 32 Hershey J M and Soskin, Samuel Substitution of "Lecithin for Raw Pancreas in the Diet of the Depancreatized Dog *Am J Physiol*, 98 74 1931
- 33 Best, C. H and Hershey J M.. Further Observations on Effects of Some Component of Crude Lecithine on Depancreatized Animals. *J Physiol.*, 75-49 1932
- 34 Best, C. H., Ferguson G C. and Hershey J M. Choline and Liver Fat in Diabetic Dogs *J Physiol.*, 79-94 1933
- 35 Barrett, H M., Best, C. H., MacLean, D L. and Ridout, J H The Effect of Choline on the Fatty Liver of Carbon Tetrachloride Poisoning *J Physiol.*, 97 103 1939
- 36 Best, C. H and Huntsman, M. E.. Effects of Components of Lecithine Upon Deposition of Fat in Liver *J Physiol.*, 75 405 1932.
- 37 Frame, E. G. Lipotropic Substances. *Yale J Biol & Med.*, 14 229 1942.
- 38 Elmao R. and Hefetz, C. J. Experimental Hypoalbuminemia. *J Exper Med.*, 73-417, 1941
- 39 Messinger W J and Hawkins, W B. Arsenamine Liver Injury Modified by Diet. *Am. J M. Sc.*, 199 216, 1940
- 40 Miller H and Whipple, G H. Chloroform Liver Injury Increases as Protein Stores Decrease. *Am. J M Sc.*, 199 204 1940
- 41 Goldschmidt, S., Vars, H M and Ravden, I S. Influence of Foodstuffs Upon Susceptibility of Liver to Injury by Chloroform and Probable Mechanism of Their Action. *J Clin Investigation*, 18 277 1939

- 42 Fagin, I D., Sahyun, M and Pagel, R. W Lipotropic Action of Parenterally Administered Amino Acids J Lab & Clin Med, 28:987, 1943
- 43 Patek, A J, Jr and Post, J, Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B-Complex. J Clin Investigation, 20:481, 1941
- 44 Fleming, R G and Snell, A M Portal Cirrhosis with Ascites, Analysis of 200 Cases with Special Reference to Prognosis and Treatment. Am J Digest Dis, 9:115, 1942
- 45 Broun, G O and Muether, R O Treatment of Hepatic Cirrhosis with Choline Chloride and Diets Low in Fat and Cholesterol J.A.M.A., 118:1403, 1942
- 46 Yater, W M Discussion of Paper by Green, C. H., J.A.M.A., 121:720, 1943
- 47 Russakoff, A H and Blumberg, H Choline as an Adjutant to the Dietary Therapy of Clinical Cirrhosis of the Liver Federation Proceedings, 3:96, 1944
- 48 Beattie, J and Marshall, J Methionine in the Treatment of Liver Damage. Nature, 153:525, 1944
- 49 Unpublished data

## LYMPHOGRANULOMA VENEREUM

ROBERT B GREENBLATT, MD \* AND PAUL L WERMER, MD †

CONTRARY to popular opinion, lymphogranuloma venereum is apparently an ancient disease since Greek, Roman, Hebrew and Arabian physicians carefully described draining buboes which coincide closely with our conception of the inguinal syndrome.<sup>1</sup> During the Dark Ages this knowledge was lost. In the great pandemic of syphilis during the sixteenth century, these buboes were again described, but attributed to syphilis. The failure of the buboes to respond to mercurial therapy aroused the suspicion of early English and French authorities that they might not be syphilitic.<sup>2,3</sup> In the latter half of the 19th century the relationship of anorectal syndrome and elephantiasis was described.<sup>4</sup> It remained for investigators of this century, especially in the last three decades, to gather together the various conditions named climatic or tropical bubo strumous or scrofulous bubo, lymphogranuloma inguinale, paradenitis, lymphopathia venereum, lupus vulvae, the fourth venereal disease, the sixth venereal disease, Nicolas-Favre disease, and prove that they were but manifestations of the same disease. The venereal origin of lymphogranuloma venereum was demonstrated for the first time during this period.<sup>5,6</sup>

This tremendous volume of investigation and interest in lymphogranuloma venereum has resulted in the development of methods which definitely place this disease within the ability of the family physician to diagnose and treat in his own office. It is important that the general practitioner recognize this, since he is the first to be consulted by the patient and upon his early diagnosis and proper institution of therapy, distressing late manifestations of lymphogranuloma venereum may be avoided.

### DEFINITION

Lymphogranuloma venereum is a systemic disease acquired venereally, the causative agent of which is filtrable. It is characterized by the appearance of a small, evanescent, often unnoticed primary lesion of the genitalia or other mucosal surface, followed by a secondary spread of the infection along the lymph channels and nodes draining the area,

---

\* Surgeon (R) United States Public Health Service, United States Coast Guard Yard Curtis Bay Maryland (Now on active sea duty with the Coast Guard.)

† Surgeon (R) United States Public Health Service, Medical Center Hot Springs, Arkansas (Now Director of the Venereal Disease Clinics, Chicago Health Department.)



with resultant subacute lymphadenitis and/or a chronic, neoformative, inflammatory reaction of the subjacent connective tissues of the invaded parts<sup>7</sup>

### ETIOLOGY

The specific causative agent of lymphogranuloma venereum is filtrable and probably belongs to a class of pathogenic entities between the virus and rickettsia.<sup>8,9</sup> Experimental animals and the yolk cells of the developing chick embryo have been successfully inoculated with the agent and the disease transmitted back to man to satisfy Koch's postulates<sup>10,11,12 18</sup> Early observers noted inclusion or Gamma bodies (0.7 to 4.0  $\mu$ ) in the cytoplasm of mononuclear cells in lymph nodes of both the human and experimental disease<sup>10,11 12</sup> Further investigation has disclosed a probable developmental cycle during the greater part of which the agent may be seen microscopically under oil immersion<sup>14,15</sup> The *elementary or inclusion body* (0.1 to 0.175  $\mu$ ) is apparently the invasive form, and must enter a living cell to continue development After penetration into the cell, these forms disappear, and no type of organism is demonstrable It is postulated that during this period the agent becomes ultramicroscopic In ten to twelve hours after inoculation, the *agent or initial body* (0.4 to 0.7  $\mu$ ), more than double the size of the inclusion body, may be seen in the cytoplasm of the invaded cells The agent bodies reproduce by fission to produce plaques enclosed in cysts within the cytoplasm The plaques then vacuolate and break up into individual forms resembling the original inclusion body This is followed by rupture of the cyst wall and cell membrane and release of the newly formed inclusion bodies to invade neighboring cells of the host tissue<sup>13,14 15 15a</sup>

A toxin is elaborated by the agent, probably accounting for the severe systemic reactions encountered occasionally in the human disease<sup>15</sup> The agent definitely produces an immunologic response in its host as demonstrated by the complement fixation test, Frei test, and use of convalescent serum in treatment. The filtrable agents of psittacosis, trachoma, inclusion blennorrhoea, human atypical pneumonia, acute meningopneumonitis, and mouse pneumonitis are closely related to the agent of lymphogranuloma venereum<sup>15a</sup>

### INCUBATION PERIOD

The primary lesion develops within five to twenty-one days after exposure, the average being seven to twelve days However, since the primary lesion is so transient, it often escapes notice, and the bubo may represent the first manifestation noted by the patient The bubo usually appears ten to thirty days after the exposure, but at times months may elapse before its appearance<sup>16</sup>

## EPIDEMIOLOGY

The disease is contracted and spread primarily by sexual intercourse and perversities. Accidental infection also plays a role, especially in the extragenital forms of the disease. Lymphogranuloma venereum is met with most frequency in tropical and semitropical countries, but has spread along the lines of commerce throughout the world, appearing especially along sea coasts<sup>17</sup>

## INCIDENCE

**Age**—The greatest number of cases occur during the period of greatest sexual activity. Children have been infected accidentally by exposure to the agent in contaminated clothing, douche nozzles and sinus discharges<sup>18</sup>. Whether there can be placental transmission of the disease is a moot question in the human host. Abortion is a frequent concomitant to lymphogranuloma venereum infection occurring early in gestation. Experimentally, the agent has been transmitted into the fetus of the infected mouse, by way of the placenta. One of us (R B G) has skin tested some fifteen infants and children of mothers known to have active lymphogranuloma venereum during gestation without encountering a single positive Frei reaction. Other investigators have found positive Frei reactions in similar cases<sup>19</sup>.

TABLE 1 —RATE OF ADMISSIONS FOR LYMPHOGRANULOMA VENEREUM PER 1000 MEAN STRENGTH, U S ARMY AND U S NAVY

Year	Army	Navy
1936	0.1	0.82
1937	0.4	1.10
1938	0.5	1.87
1939	0.4	2.11
1940	0.5	1.54

Data from Annual Reports of the Surgeon General U S Army 1937-41 Statistics of Diseases and Injuries.

**Race**—All races exposed to the disease are susceptible. In the University of Georgia Clinics, a series of 197 cases showed but thirteen white infections to 184 colored, a ratio of 1:16. Other observers also report high incidence in the negro race<sup>20, 21, 22</sup>.

**Occupation**—In keeping with the preponderance of cases along the sea coasts, sailors contract the disease with comparative frequency. In Army and Navy statistics this is startlingly apparent, the Navy rates per 1000 men being three times as high as the Army rates (Table I). In females the prostitute class shows the highest incidence of infection.

**Sex**—The reported sex incidence seems to favor the male, but this probably is more apparent than real. Poor reporting and nonrecog-

nition of the disease make any statistics on incidence extremely vulnerable to error. In the University of Georgia Clinics greater incidence has been observed in the female (Table 2). The epidemiology of the disease itself should argue against a differential sex ratio.

TABLE 2—AGE AND SEX INCIDENCE OF LYMPHOGRANULOMA VENEREUM IN 197 CONSECUTIVE CASES AT THE UNIVERSITY OF GEORGIA CLINICS

Age	Male	Female	Age	Male	Female
0-10	0	2	41-50	5	9
11-20	19	16	51-60	1	4
21-30	44	59	Total	79	118
31-40	10	28			

#### INFECTIOUSNESS AND PERIOD OF COMMUNICABILITY

The disease must be considered infectious while an open lesion or discharge from any source is present. Even chance contact of a mucosal surface with a contaminated article is sufficient to infect. This has been demonstrated experimentally by insertion of a contaminated enema tip into the lower bowel of the chimpanzee with resultant infection.<sup>23</sup> Sexual exposure to an open case almost inevitably is followed by infection. Even in the face of clinical recovery, the agent has been demonstrated to persist for twenty-one years and retain its infectiousness.<sup>24</sup> In the absence of open lesions the vaginal secretions have been shown to be infective.<sup>25, 26</sup> It is reported that practically the entire population of a Greek island was infected following the introduction of the disease by a single, infected prostitute.<sup>27</sup>

#### CONTROL

In considering incidence and control of lymphogranuloma venereum, it is particularly unfortunate that the disease is not on the list of communicable diseases for which notification is required by the states.<sup>28</sup> No accurate estimation of incidence or adequate epidemiologic investigation is possible under these circumstances. In 3000 admissions to the United States Public Health Service Medical Center in Hot Springs, Arkansas, between 1937-9, forty-nine cases of lymphogranuloma venereum were found, an incidence of 1.6 per cent.<sup>22</sup> This report is felt to be lower than actual incidence in this group since routine Frei tests were not performed and the etiology of rectal stricture not fully investigated during this period. Furthermore, it represents incidence not in the general population, but in a sexually promiscuous class with an extremely high index of venereal infection.

#### CLINICAL ASPECTS

**Location and Character of Primary Lesion**—The most common site of the primary lesion in the male is the coronal sulcus, followed by the

prepuce, glans, shaft and urethra. The most common sites in the female are the posterior vaginal wall and the region about the fourchette,<sup>20</sup> although it may appear on any part of the external genitalia. The inoculatory lesion may be either (a) a small erosion, (b) an infiltrated papule, (c) a herpetiform vesicle or ulcer.

The ulcer is small and shallow with ill defined edges, the base whitish gray, it is painless and often surrounded by an area of erythema. The lesion is soft on palpation, not infiltrated. It heals spontaneously in three to five days.<sup>29 30 31 32</sup> Its location, painlessness and transitory, evanescent nature often cause the primary lesion to be overlooked by the patient. Very often, after the disappearance of the primary lesion and coincident with the inguinal bubo, a secondary ulceration appears on the genitalia which is often mistakenly considered as the primary lesion (Fig 134)



Fig 134—Evanescent primary lesion (A) of lymphogranuloma venereum which was followed in three weeks by an ulceration of the shaft of the penis simultaneous with bilateral buboes (B)

**Symptomatology**—The lymph drainage area of the primary lesion is the determining factor in the progress of lymphogranuloma venereum. The course may be acute, subacute, chronic or latent. Exacerbations and remissions may occur. Lymphogranuloma venereum is a systemic disease and severe constitutional symptoms may be present during the early, insidious spread to the regional lymphatics. Fever, chills, sweats, joint pains, vague abdominal aches, anorexia and occasionally meningism or a typhoidal state may occur.<sup>30 33</sup> Recently several cases of meningoencephalitis have been reported.<sup>34</sup> A fleeting arthritis is said to occur in 10 per cent of the cases which have persisted over a period of several months.<sup>17</sup>

**Clinical Varieties.**—Both genital and extragenital varieties of the disease occur.

## I GENITAL VARIETIES

(A) *Inguinal Syndrome*—Ten to thirty days after the inoculatory exposure, one or more discrete, movable, tender nodes may be felt in the inguinal region (Fig 135) The inflammatory process may progress for several days and then spontaneously regress in 20 to 25 per cent of the cases<sup>35</sup> Usually the process continues to spread, involving all the nodes in the group and extending to the surrounding connective tissue to set up a periadenitis The buboes become quite noticeable, bulging out the skin paralleling the inguinal groove The mass of nodes may be lobulated, oval or markedly elongated, and sausage-shaped The skin becomes adherent and often takes on a violaceous hue

*The Sign of the Groove*—Enlargement of nodes above and below the inguinal fold produces a distinct groove (Fig 136) which is almost pathognomonic of lymphogranuloma venereum<sup>36</sup> The buboes may

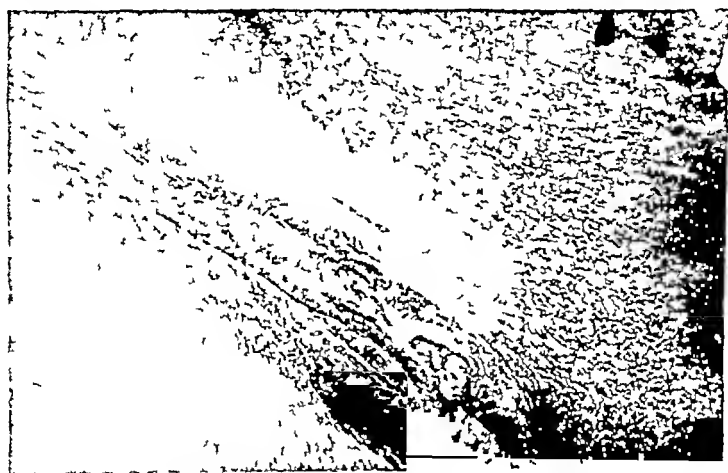


Fig 135—Inguinal buboes—upper right about to rupture, lower, draining

remain indurated and nodular for many months, or irregular areas of softening occur, succeeded by formation of multiple fistulas draining a grayish, thin pus Occasionally the suppuration results in a unilocular abscess Inguinal adenopathy is generally unilateral, but is bilateral in about a third of the cases It occurs with more frequency in the male<sup>17</sup> This variation is due to the difference in lymphatic drainage of the sexes Lymph drainage of the penis is to the inguinal and iliac nodes<sup>30 87</sup> In the female only the clitoris, urethra and anterior part of the vulva are drained by these nodes, thus only primary lesions of these areas can produce the inguinal syndrome in the female Nevertheless it occurs with more frequency in females than commonly reported In the University of Georgia clinics ninety-six cases of lymphogranuloma venereum in the female were reviewed, of these patients twenty-nine had buboes at admission and four had a history of buboes—an incidence of 34.3 per cent<sup>16</sup> In seventy-seven male pa-

tients the syndrome occurred fifty-six times, an incidence of 72.7 per cent. Healing is accompanied by scarring, wrinkling and dimpling of

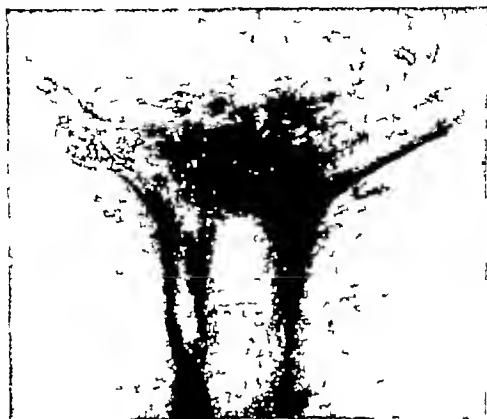


Fig 136—Sign of the groove.



Fig 137—Bubonuli, small abscesses along the course of the lymphatics of the penis.

the skin about the sinus opening.<sup>28</sup> Constitutional symptoms often occur early in the inguinal syndrome.

(B) **Genital Syndrome**—After disappearance of the primary lesion, massive multiple ulcerations of the penis or vulva may develop. Hypertrophy and hyperplasia of the tegument and underlying connective tissue due to local lymph stasis and dilatation of lymph channels may follow. In the male, *bubonuli*, small abscesses along the shaft of the penis following the course of the lymphatic channels (Fig 137), occasionally occur. With sufficient lymph stasis, massive elephantiasis of the penis may ensue. In the female, elephantiasis occurs with more frequency than in the male. Elephantiasis, with ulcerations of the vulva and perianal region, constitute the syndrome called *esthiomene* (Fig 138). The enlargement may affect any or all parts of the external genitalia. On palpation the parts are turgid, and rubberlike in consistency, due to the chronic, inflammatory, neoformative reaction. The ele-



Fig 138—*Esthiomene*—elephantiasis and ulceration of the vulva and lobulated anal growths

phantiasic surfaces may be smooth, verrucose or corrugated with a "cobblestone-like" appearance (Fig 139). Pedunculation of the elephantiasic labium and clitoris are quite frequent (Fig 140). The ulcerative lesions have a pearly, translucent, granulomatous base with uneven projecting tufts of granulation tissue. The ulcers may involve the vaginal mucosa and progress to form rectovaginal fistulas. On healing, cicatricial contracture may cause vaginal stricture.

(C) **Anal Syndrome**—Polypoid and lobulated growths about the anal orifice occur either alone or accompanying the genital or rectal syndrome. In the early stages of this syndrome, indurated rubbery anal tabs of opalescent hue are present and may be mistaken for hemorrhoids (Fig 141). The term "lymphorrhoids" has been suggested and seems apt and descriptive for these lobulated anal tabs caused by



Fig 139—Elephantiasis of clitoris, labia majora and rectal stricture. Note cobblestone appearance of granulation tissue.



Fig 140—Genito-anorectal syndrome. Note marked elephantiasis of clitoris and labia, lymphorroids. This patient also had rectal stricture.

lymph stasis. The anorectal syphilomas described by Fournier in 1875 were in all probability the lymphorrhoids of the anal syndrome.<sup>7</sup>



(D) **Rectal Syndrome**—In the male, this syndrome follows primary infection of the rectal mucosa, most usually acquired as a result of sodomy<sup>39, 40</sup> Its appearance requires careful and judicious approach to the possibility of irregular sex practice At the United States Public Health Service Medical Center, one recent instance of rectal stricture in the male was acquired while the victim was serving a sentence in the penitentiary of a nearby state This patient claimed that sodomy was practiced upon all new inmates by gangs of fellow prisoners



Fig 141—Lymphorrhoids—hemorrhoid-like anal tabs caused by dilatation of anal lymphatic channels

In the female, the rectal syndrome is much more common, and while it may occur as a result of sodomy, it most usually occurs as a result of primary infection of the vagina, or of the posterior two thirds of the vulva The lymph drainage of these areas is to the pararectal glands<sup>30, 37</sup> In children and adults the syndrome has followed the use of an infected enema tip<sup>17</sup> Proctitis is indicative of a primary locus of infection in the rectal mucosa, its absence indicates the infection began outside the rectal wall<sup>41</sup> This finding may be utilized to classify the rectal syndrome into its various components

## Primary in Rectal Mucosa\*

- 1 Proctitis
- 2 Proctitis with rectal stricture

## Primary Outside Rectal Mucosa

- 1 Rectal Stricture
- 2 Rectal Stricture with abscess formation

\* Most male cases in this group

## INFECTION ORIGINATING IN RECTAL MUCOSA

1 *Proctitis*—This condition usually begins with small rectal hemorrhages. Proctorrhea with a purulent discharge is found in practically every case.<sup>42</sup> The discharge is the most annoying symptom, since *pain is very seldom experienced*. The proctoscopic examination may reveal an edematous, boggy, redundant mucosa, or a granulomatous, ulcerative lesion, or polypoid verrucous hypertrophy of the mucosa. Residual polypoid growths may persist long after the infection apparently has resolved. Therefore, rectal growths which prove not to be neoplastic on histopathologic study, should be restudied with lymphogranuloma venereum in mind as a causative agency.<sup>43</sup>

2 *Proctitis with Rectal Stricture*—If untreated, the proctitis progresses, burrowing deeper into the bowel wall to encircle the entire lumen. When healing ensues, cicatricial contraction of the scar tissue gradually obliterates the lumen.

## INFECTION ORIGINATING OUTSIDE RECTAL MUCOSA

1 *Rectal Stricture*—This condition may be found without any other manifestation of lymphogranuloma venereum and often in the absence of any history of a primary lesion or bubo. The pararectal nodes are the site of secondary involvement from the usual genital, primary lesion. They may be seen at laparotomy as groups of pearly, bean-shaped nodes studding the bowel wall. Retrograde extension of the infection along the lymphatic channels involves the outer coats of the bowel. Subsequent lymph stasis, edema and ultimate organization produces rectal stricture by cicatrization with gradual, progressive reduction of the lumen of the gut.

2 *Rectal Stricture with Abscess Formation*—Untreated, the infection of the pararectal nodes and the perirectal tissues progresses, as in the inguinal syndrome, to abscess formation. Unlike the inguinal glands, the pararectal glands lie deep in the tissues and have no easy means of evacuation. The multiple abscesses produced, burrow in many directions through the perirectal-vaginal tissues, to produce sinus tracts and fistulous openings in the vagina, rectum, ischio-rectal and perianal areas. The fistulas always originate below the stricture, and their association with the pararectal glands, has been demonstrated by injection with iodized oil and radiography.<sup>37 44</sup> The infection may run its course and healing take place. Usually it persists, running a chronic course with widespread diffusion of the process throughout the pelvic lymph spaces, channels and lymph nodes. The rectum, vagina, uterus

and adnexa may be fixed and a "frozen pelvis" ensue. The lymphangitis and lymphadenitis with blockage of lymph drainage may result in other syndromes presenting themselves, i.e., elephantiasis, stricture of the urethra and vagina.

**RECTAL STRICTURE—SPECIAL CONSIDERATIONS**—The rectal stricture of lymphogranuloma venereum is of a cylindric, constricted "rubber hose" variety. It is usually situated 3 to 8 cm above the anal sphincter. Its average length is 4 cm, although strictures involving the whole rectum and the colon have been reported.<sup>28</sup> Early, the walls have an "india-rubber" consistency, later, more induration follows until the wall becomes semi-rigid as fibrous tissue replaces the edematous and indurated tissue. Untreated strictures are progressive, the lumen may become so constricted that ileostomy or colostomy must be performed. Pain is a symptom of primary importance in cases of proctitis, since its appearance probably marks the beginning of stricture formation. Constipation parallels the degree of stricture, the stools become more ribbon-like with the stricture progression, abdominal cramps and tenesmus develop with the restriction of fecal passage. The progress of the constriction is slow<sup>17</sup> and is a late manifestation when proctitis is absent.<sup>42</sup> When proctitis is present, strictures have been reported to begin within three months of the onset of proctorrhea.<sup>17</sup>

Other portions of the gastrointestinal tract may be involved by lymphogranuloma venereum. One recent report of a series of cases describes inflammatory lesions of the cecum and colon, enlarged mesenteric lymph nodes, multiple hepatic abscesses, sterile fibrinous peritonitis and perforation of an ulcer of the colon.<sup>45</sup>

Ulcerative colitis, with typical bloody rectal discharges, has been reported. The lesions start in the rectum and usually remain confined to the distal segments of the large intestine. Rectal stricture and multiple small sinuses proceeding from the mucous membrane to the deeper structures are often concomitant findings.<sup>46</sup>

**Rectal Stricture and Pregnancy**—While rectal stricture is not necessarily a contraindication to vaginal delivery, its presence associated with perirectal fibrosis, soft tissue masses or fixation of the posterior vaginal wall may lead to rupture of the uterus. Intraperitoneal rupture of the rectum has also occurred in attempted breech extractions when the aftercoming head passed over the stricture.<sup>46, 47</sup>

**(E) Urethral Syndrome**—The first symptom is a purulent discharge containing many polymorphonuclear cells but no visible pathogenic organisms. All cases of "nonspecific" urethritis, with a history of sexual exposure shortly before the symptomatology develops, should have repeated Frei tests to eliminate the possibility of lymphogranuloma venereum as a causative agency. Urethral strictures, ulcers and fistulas may supervene. Acute and chronic prostatitis, seminal vesiculitis and epididymitis may occur in the male. In the female, esthiomene often is associated with bladder neck deformation and late in the course of the

disease involvement of the perirectal and parametrial tissues, and the deep nodes may cause displacement, compression or invasion of the genitourinary structures <sup>47a</sup>

## II EXTRAGENITAL LYMPHOGRANULOMA VENEREUM

Apparently any mucous membrane exposed to the agent of lymphogranuloma venereum may become the site of the primary lesion. The secondary manifestations will develop in the lymph drainage area of the initial locus, because of the lymphotropism of the disease. Various perverted sexual practices have led to infections of the tongue, <sup>48</sup> tonsil, <sup>49</sup> mucous membrane of the mouth, the hypopharynx, larynx<sup>50</sup> and the conjunctiva (Parinaud's conjunctivitis) <sup>51, 52</sup> Axillary buboes have developed following accidental inoculation of the finger during opera-

TABLE 3 —FREQUENCY OF CLINICAL MANIFESTATIONS OF  
LYMPHOGRANULOMA VENEREUM

Type of Disease	New York Hospital		University of Georgia Hospital Clinics	
	No of Cases	Per Cent	No of Cases	Per Cent
Anorectal	145	59.9	46	30.7
Inguinal	60	24.8	77	51.3
Genital	28	11.7	26	17.3
Asymptomatic	6	2.5		
Urethral			1	0.7
Miscellaneous*	3	1.1		

\* Includes one case each of carcinoma of rectum, cystitis and granulomatous pelvic masses (Courtesy of E. R. Squibb & Sons, Monograph Lymphogranuloma Venereum)

tive procedures <sup>50 53 54</sup> Laboratory workers handling high concentrations of the agent have developed generalized symptoms, septic type fever with chills, sweats, joint pains and headache <sup>55</sup> Cervical adenitis is occasionally a concomitant of these cases Meningeal infections have been reported <sup>54 56, 57</sup>

It should be emphasized that, while syndromes have been presented as separate entities, clinically they may occur separately or in any combination

### CLINICAL COURSE

The variants of host susceptibility and agent virulence lead to wide latitude in clinical course. The disease may be so minimal in some that the patient is never aware of the infection In others the disease may be so chronic as to persist for years, with residual lesions so incapacitating and debilitating as to make the patient a possible public charge



Fig 142 —Marked elephantiasis and pedunculation of labia minora, labia majora and clitoris



Fig 143 —Genital syndrome—elephantiasis of penis and scrotum, draining sinuses of scrotum

In one patient a syndrome may progress with great rapidity, in another, with indolence, and in a third it may remit spontaneously. The

female patient, because of her lymphatic drainage, may present simultaneously, or successively, various syndromes. The fibroblastogenic diathesis of the Negro frequently results in marked neoformative reaction of the tegument and underlying connective tissue to the agent of lymphogranuloma venereum, with formation of gargantuan hypertrophy and elephantiasis (Fig. 142)<sup>58</sup> In the white race, elephantiasis is a rare condition. Since lymphogranuloma venereum is a subacute inflammatory process causing hypertrophy and neoplasia, malignancy may supervene. Anaplasia and metaplasia occur with more frequency than in the other granulomatous processes.<sup>60 60 61</sup>

### DIAGNOSIS

1 **History**—If obtainable, the history of an evanescent, herpetiform lesion followed by the development of signs and symptoms suggestive of one of the syndromes of lymphogranuloma venereum is a most valuable adjunct to diagnosis.

2 **Clinical Picture**—A subacute, inflammatory neoformative, granulomatous process, or "sign of the groove" enlargement of regional lymph node or elephantiasic lesions or fistulous tracts discharging grayish pus, suggest lymphogranuloma venereum.

3 **The Frei Test**<sup>62</sup>—This intradermal test represents the most important single aid to diagnosis. It usually becomes positive by the time of bubo formation (ten to thirty days after infection). Originally human bubo pus was sterilized and diluted to produce an antigen. This method had the disadvantage of the lack of a control to eliminate non-specific reactions. Later a mouse brain antigen was devised which provided an unlimited supply of test material and had the advantage of a control.<sup>62, 63 64</sup> The disadvantages of mouse brain antigen were non-specific reactions, low concentration of the agent and the possibility of sensitizing the patient to the antigen.<sup>65 66 67</sup> Recently an antigen has been perfected from the infected yolk cells of the chick embryo.<sup>68 69</sup> This preparation yields high concentrations of antigen, has an available control material and elicits the least number of false positive reactions.<sup>17 21 62 63 64, 65 70 71 72 73 74</sup> The test is performed by the intradermal injection into the forearm of 0.1 cc. of the antigen and 0.1 cc. of the control. The test should be read at forty-eight hours and preferably again at seventy-two hours. In reading the test, erythema or flare should be disregarded. A positive test is indicated by an indurated, inflammatory nodule measuring at least 5 to 6 mm. along its greatest diameter. Mensuration should be done with an accurate millimeter scale from the margin of *beginning induration* to the *end of the induration*. Positive tests tend to persist for many days, while false positives tend to disappear within seventy-two hours.<sup>70</sup> A negative test, in what seems a typical case, may be due to anergy<sup>87</sup> or the test may have been performed too early in the disease. The area tested should be observed for a week, as late or delayed reactions sometimes

occur and if still negative, repeat the test. Necrosis, or the development of a bleb or vesicle in the center of the nodule, indicates a highly positive reaction. The control reaction should not exceed 3 mm. A positive test may be reversed by intensive, early, sulfonamide therapy,<sup>55</sup> but in well developed or chronic cases the test remains positive for life. In extreme debility or the moribund state, anergy may result.<sup>36</sup>

**4 Biopsy**—The histopathologic picture of lymphogranuloma venereum is highly suggestive of the diagnosis, but not specific. In doubtful cases, where multiplicity of infections may be present, it is of considerable value. In the bubo form, inflammatory and suppurative changes are found in the lymph nodes and perilymphoid tissues. There is a combined polymorphonuclear and granulomatous reaction characterized by minute foci of necrosis or micro-abscesses surrounded by macrophages and an occasional giant cell. In elephantiasis, there is pronounced peritubular infiltration with plasma cells and lymphocytes, accompanied by fibroblastic activity, dilated lymphatics, in some cases with giant cells of foreign body type and foci of suppuration similar to those encountered in buboes.<sup>61, 76</sup> In the benign neoplastic form of lymphogranuloma venereum, biopsy is a great aid in ruling out malignancy.

**5 Autoinoculation**—Bubo pus removed by aspiration under sterile precautions rubbed into a scarified area of the thigh *will not* produce ulceration in lymphogranuloma venereum, while in chancroid disease it frequently will produce a characteristic chancroidal ulcer.<sup>30</sup>

**6 Complement Fixation Test**<sup>70 77 78</sup>—Judiciously utilized, the complement fixation test is considered to have value in early diagnosis. A concentrated, purified chick-embryo antigen is now available commercially for complement fixation. Unfortunately, cross reactions occur with syphilis and members of the psittacosis-lymphogranuloma venereum group.<sup>79, 80 81</sup> The complement fixation test becomes positive earlier than the intradermal test. When repeated Frei tests result in doubtful reactions, a test of high titer dilution (1-80 or higher) is suggestive of lymphogranuloma venereum. Titers below 1-80 must be regarded with doubt. Therapy apparently lowers the titer, but does not change the positive complement fixation reaction. Greater specificity is necessary before major reliance may be placed on this test.

**7 Inverted Frei Test**<sup>82</sup>—In certain instances a negative Frei test is obtained even in the presence of a suppurative bubo. The pus aspirated from a bubo, macerated and ground up lymph nodes or infected tissue may be made into an antigen and injected into known cases of lymphogranuloma venereum, particularly persons with rectal stricture. Incontestable positive reactions in persons with proved lymphogranuloma venereum and absolutely negative reactions in normal controls and in persons with allergy to chancroid must be obtained, if the inverted Frei test be accepted as of diagnostic significance.

*Preparation of Frei Antigen From Bubo Pus*—The fluctuant bubo is aspirated under sterile conditions using a 16-gauge needle. The surface of the bubo is first prepared by shaving and cleaning with skin disinfectants such as alcohol and ether or iodine. Patients with positive blood serologic tests for syphilis, positive chancroid skin test, or fistulization of the bubo should not be used. Spreads and routine cultures of the aspirated pus are made to rule out the presence of bacteria.

The pus is diluted with 4 parts of sterile normal saline solution as soon as possible after aspiration. The diluted material is immersed in a water bath of 58 to 60 degrees C. for two hours and on the next day for one hour. Further tests for sterility by spread and culture are made. If all bacteriologic tests are negative, phenol (0.25 to 0.5%) is added to the antigen as a preservative.

**8 Blood Chemistry**—The blood picture is not characteristic, moderate secondary anemia has been reported and the sedimentation rate is increased.<sup>83 84</sup> Blood chemistry presents one test of occasional value in early diagnosis—the increase in serum proteins, especially globulin (up to 9 per cent).<sup>87 88 83 80 87 88 89</sup> Granuloma inguinale and other chronic diseases cause marked change in the serum globulin content and reduce the value of this finding.<sup>84 88</sup>

#### DIFFERENTIAL DIAGNOSIS

**Syphilis**—Syphilis may imitate the primary and secondary ulcers of lymphogranuloma venereum, the buboes of the inguinal syndrome and the urethral syndrome. To further complicate the situation many coincidental infections of these two conditions exist. Darkfield examination with identification of the *Treponema pallidum*, or a positive serologic test, establishes the diagnosis of syphilis but does not rule out the possibility of coexistent lymphogranuloma venereum. This is especially true in the face of a positive Frei test, and of lesions and buboes that persist despite antisyphilitic therapy. Repeated negative darkfield examinations of ulcers and of node puncture material as well as repeated negative serologic tests for syphilis rule out this diagnosis.

**Gonorrhea**—The urethral discharge, cutaneous ulcers<sup>90</sup> and proctitis of gonorrhea must be differentiated from lymphogranuloma venereum. The Frei test very often is not positive for some time after the onset of the urethral discharge in the urethral syndrome. Repeated negative cultures (five or more) and negative spreads for the gonococcus must be obtained before ruling out this diagnosis. A positive Frei and a positive complement fixation test validate the lymphogranuloma venereum diagnosis and eliminate *nonspecific urethritis*.

**Chancroid**—The ulcerative lesion and bubo of chancroid may be differentiated from lymphogranuloma venereum by the autoinoculability of chancroid and by demonstration of the *Ducrey* bacillus. The positive Frei and complement fixation tests are aids in establishing the diagnosis of lymphogranuloma venereum. The skin test for chancroid and the Frei test often show simultaneous reactions when only one of the diseases is clinically present.<sup>91 92</sup> These are not necessarily to be considered as false positives, since the test may represent previous in-



fection<sup>93</sup> If only one skin test is positive, then it serves to differentiate between the diseases The ulcers of lymphogranuloma venereum are usually painless, if uncomplicated, while those of chancroid are often painful, phagedenic, and acutely inflamed

**Granuloma Inguinale**—The positive Frei test, positive complement fixation test, as well as the failure to demonstrate Donovan bodies in biopsy or scrapings after repeated trials, establish the diagnosis of lymphogranuloma venereum The inguinal swelling encountered in granuloma inguinale is actually a subcutaneous, granulomatous process, individual nodes cannot be differentiated in this mass Both entities may, and frequently do, occur together Secondary elephantiasis, indurative in type, is not uncommon in granuloma inguinale

TABLE 4—VARIOUS CONDITIONS FROM WHICH THE SYNDROMES OF LYMPHOGBANULOMA VENEREUM MUST BE DIFFERENTIATED

Ulcers, Primary and Secondary	Inguinal Syndrome	Anorectal Syndrome	Genital Syndrome	Urethral Syndrome
Syphilis	Syphilis	Malignancy	Filariasis	Gonorrhea
Herpes progenitalis	Granuloma inguinale	Hemorrhoids	Kraurosis	Intraurethral chancre
Chancroid	Tuberculosis	Gonococcal proctitis	Fibroma	Nonspecific urethritis
Granuloma inguinale	Chancroid	Rectal schistosomiasis	Malignancy	
Gonorrhea	Hodgkin's disease	Polyposis	Urogenital schistosomiasis	
Fusospirochetosis	Tularemia			
Malignancy	Actinomycosis			
	Regional adenitis			

**Herpes Progenitalis**—This eruption is usually preceded by a prodromal itching and a sensation of heat, rarely by pain This is followed by the appearance of single or multiple pinhead-sized vesicles which rupture and occasionally coalesce to form a superficial lesion with shaggy, irregular edges Occasionally enlarged, tender nodes are found which may reach bubo proportions The history of previous crops of herpetic vesicles may be obtained in most instances The Frei test and positive complement fixation test establish the diagnosis of lymphogranuloma venereum

**Fusospirochetosis**—In primary fusospirochetosis the early lesions have a moist, pinkish, glazed appearance When ulceration gets under way it is rapid and destructive The spirillum and vibrio of Vincent may be demonstrated readily in spreads stained with Wright's stain or by darkfield examination Primary fusospirochetosis may be responsible for an erosive and gangrenous balanitis and may resemble a phage-

denic, chancroidal infection. Genital lesions frequently become contaminated with fusospirochetes, and occasionally these saprophytic organisms play a role in the destructive or recalcitrant nature of the underlying infection whether it be syphilis, chancroid, granuloma inguinale or lymphogranuloma venereum.<sup>94</sup> Fusospirochetes are not necessarily destroyed by intravenous arsphenamine therapy, intramuscular bismuth therapy, or by antimony compounds. These secondary invaders are best treated by topical applications of arsphenamines or by oxidizing agents such as *sodium perborate* or *zinc peroxide*. A mixture found to be very useful in the treatment of fusospirochetosis contains 7 to 10 per cent of arsphenamine in equal parts of cod liver oil and glycerine. Some analgesic may be added to this mixture when its application proves painful.<sup>95</sup> At the U.S.P.H.S. Medical Center penicillin parenterally and locally has proved of worth in a small series of cases. Dusting with vioform powder has been helpful in controlling several recalcitrant lesions.

**Malignancy.**—Malignancy must be differentiated from the ulcers of esthiomene, anorectal syndrome, genital syndrome and the inguinal syndrome. This is best done by histopathologic study of biopsy specimens.<sup>43</sup>

**Tuberculosis.**—Biopsy of the tissues will show typical tubercle formation, and the demonstration of tubercle bacilli in spreads and transmission of the disease to animals by inoculation establish the diagnosis of tuberculosis.

**Filariasis and Schistosomiasis.**—Members of our armed forces are being exposed to these conditions in the South Pacific, Egypt, Africa and the Orient. *Filaria bancrofti* causes elephantiasis of the lower extremities and scrotum, less frequently of the vulva. Demonstration of filaria in stained, thick blood films or in the lymph from the elephantiasis areas establishes the diagnosis of filariasis.<sup>95</sup> Elephantiasis, common among natives, does not seem likely to develop among our troops, judging from present trends.<sup>96</sup>

**Schistosomiasis.**—Schistosomiasis may simulate the genital and anorectal syndromes of lymphogranuloma venereum. Actual elephantiasis of the penis with fistulous openings draining purulent material may result from this parasitic disease. The demonstration of the typical ova in the urine and feces serves to establish the diagnosis.<sup>97</sup>

**Tularemia, Hodgkin's Disease and Regional Adenitis.**—These may simulate the inguinal bubo of lymphogranuloma venereum. Tularemia may be differentiated by its specific agglutination reaction and demonstration of the specific organism in the suppuration.<sup>98</sup> Hodgkin's disease may be differentiated by the biopsy and histopathologic study, regional adenitis by demonstration of the causative organism or the presence of local infection.

**Actinomycosis.**—Actinomycosis may be differentiated by demonstration of the ray fungus in the discharges from the sinuses.

## TREATMENT

**Chemotherapy**—Sulfonamides are the treatment of choice in lymphogranuloma venereum. The effectiveness of sulfonamide therapy is inversely proportional to the duration of the infection. Utilized in the early stages of any syndrome of lymphogranuloma venereum the progress of the condition is arrested, ulcerative processes heal, the buboes regress, proctitis ceases, the urethral discharge improves<sup>99</sup>. Continued long enough, the sulfonamides produce clinical regression or arrest in 80 per cent of the inguinal cases and marked improvement in the anorectal cases<sup>17</sup>. Regardless of the stage of lymphogranuloma venereum, sulfonamide therapy is often effective in checking pain, discharge and progression<sup>99</sup>.

Sulfathiazole and sulfadiazine seem to be the drugs of choice of most investigators,<sup>32, 99 100, 101 102</sup> although sulfaguanidine and sulfasuxidine have been suggested for the rectal syndrome because of their poor absorption<sup>36, 103</sup>. Sodium sulfanilyl sulfanilate has been utilized by another group of investigators for rectal syndrome with apparently excellent results<sup>104 104a</sup>. A course of 4 gm of sulfathiazole daily for two weeks, alternating with rest periods of two to three weeks, continued through a minimum of a year has been found effective in anorectal disease with proctitis<sup>102</sup>. Recurrences have been brought under control with additional sulfathiazole. Lymphogranuloma venereum conjunctivitis has been cured by sulfadiazine<sup>105</sup>. The average early case at the Medical Center is given 1 gm of sulfathiazole four times daily for a week or ten days, then, after a week's rest period, an identical, second course. If indicated by the clinical response, more courses may be given. The average total dosage varies between 56 to 80 or more grams. A white blood count and differential should be done weekly. Complications observed have been agranulocytopenia, mild fever and dermatitis medicamentosa, all of which cleared on withdrawal of the drug.

A note of caution must be added concerning the efficacy of the sulfonamides in rendering the lymphogranuloma venereum agent avirulent. Investigators have found that dosages of sulfonamides sufficient to protect inoculated mice against the agent apparently do not render the agent avirulent. Successful transmission of the disease to other mice has occurred following inoculation of brain substance from "protected" mice<sup>106 107 108</sup>. Treatment apparently lowers the concentration of the agent but does not affect its virulence<sup>108</sup>. The future epidemiology of lymphogranuloma venereum should reveal whether we are producing asymptomatic carriers by sulfonamide therapy.

The advent of *penicillin* in the therapy of syphilis has given an opportunity to watch its effect upon lymphogranuloma venereum in coexistent infections. In a series of cases observed at the United States Public Health Service Medical Center in Hot Springs, dosages of penicillin varying from 600,000 Oxford units to 2,400,000 units failed

to affect the ulcers or the buboes of lymphogranuloma venereum. One case actually developed inguinal buboes while receiving 2,400,000 units of penicillin (PLW). In all these cases the sulfonamides subsequently caused clinical response. Evidently, in the dosages used, penicillin has no effect upon lymphogranuloma venereum.

**Aspiration**—Fluctuant buboes should be aspirated—never incised. Where local complaints call for immediate relief or where perforation is imminent, the pus should be aspirated. This gives the same instantaneous effect, creates a better wound and furnishes sterile material for Frei antigen and the inverted Frei test.

**Vaccinotherapy**—Vaccinotherapy has been utilized by (a) subcutaneous,<sup>90 100 110</sup> (b) intracutaneous<sup>88 99 111 112</sup> and (c) intravenous routes,<sup>90 113 114 115 116</sup> or (d) combined with sulfonamides<sup>117 118</sup>. Ascending dosages of vaccine are injected at five-day to weekly intervals, beginning with 0.05 cc and increasing 0.01 cc, as indicated, to the maximal dosage of 1 cc. The combined form of therapy has been recommended in the more chronic forms of the disease.<sup>90 109</sup> In the sulfasensitive individual vaccinotherapy may be the only available method of treatment.

**Convalescent Serum**—Five cubic centimeters of convalescent serum was injected intramuscularly at weekly intervals, by one group of workers with apparent good results.<sup>119</sup>

**Surgery**—The removal of the polypoid pedunculated tumors and elephantiasic vulvae is often advisable. Healing readily takes place, but recurrences several years later have been noted. Matted nodes that have remained indurated for months may require total extirpation.<sup>111 116 120</sup> This procedure is attended by the danger of lymphatic obstruction and chronic elephantiasis of the pudenda, as an operative complication. As a general practice, excision should be deprecated and aspiration preferred. Ileostomy and colostomy may be necessary due to intestinal obstruction caused by rectal stricture.

**Management of Rectal Stricture**—(a) The *sulfonamides* reduce the pain, proctorrhoea and other secondary manifestations of rectal stricture. Continued over long periods of time, with intervening rest periods, a few cases have been reported to go on to clinical "cure". (b) When chemotherapy is combined with *vaccinotherapy*, excellent results have been reported.<sup>113 114</sup> (c) In addition to chemotherapy the stricture should be gently *dilated* at weekly intervals. This may be accomplished by manual or mechanical dilatation (Hegar dilator). (d) *Physiotherapy* in the form of long or short wave diathermy has proved effective in softening the inflammatory process and relaxing the stricture. Constipation is often markedly improved after dilatation and physiotherapy. If dilatation is so painful as to preclude the cooperation of the patient, caudal block or general anesthesia may be utilized to dilate the stricture thoroughly. Gentle manipulation must be employed to prevent further damage and scarring. Unless manual

dilatation is performed at weekly intervals for several months, recurrence of the stricture takes place Sulfonamide therapy should be instituted immediately following surgical dilatation, satisfactory and permanent results have been observed<sup>112</sup> (e) When strictures are beyond the reach of the examining finger, colostomy may be a justifiable procedure It must be remembered that if fibrous tissue has completely replaced inflammatory tissue, clinical cure cannot be accomplished, only clinical improvement may be attained

### CONCLUSIONS

1 Lymphogranuloma venereum in its early uncomplicated stages can be diagnosed and treated by the general practitioner in his office

2 It occurs with greatest frequency along seacoasts, is often associated with other venereal diseases and in the United States is relatively much more frequent in the Negro race

3 It is highly infectious and is communicable while an open lesion or draining sinus exists It is a systemic disease

4 Diagnosis is based upon the clinical picture, a positive Frei test and a positive complement fixation test (titer 1-80 or higher)

5 It must be differentiated from the other venereal diseases, tuberculosis, malignancy and some exotic conditions

6 The sulfonamides, preferably sulfathiazole and sulfadiazine, are the treatment of choice In chronic cases vaccinothrapy may be combined with sulfonamides

7 Penicillin in dosages from 600,000 to 2,400,000 Oxford units has not proved of worth in treatment of lymphogranuloma venereum

8 Surgery should be conservative, confined to removal of elephantiasic and polypoidal growths

### BIBLIOGRAPHY

- 1 Hellerstrom, S Acta dermat-venereol Supp 1, 1929, pp 5-224
- 2 Wallace, W Treatise on Venereal Disease and Its Varieties London, Burgess and Hill, 1833, p 371
- 3 Chassaignac, C M E Traite Pratique de la suppuration et du drainage chirurgical Paris, V Masson, 1859, p 354
- 4 Fournier, A Lesions tertiares de l'anus et du rectum, Paris, 1875
- 5 Durand, M., Nicolas, J and Favre, M Bull et mem Soc méd d hôp de Paris, 35 274, 1913
- 6 Frei, W Berl klin Wchnschr., 4 2148, 1925
- 7 Greenblatt, R B., Sydenstricker, V P and Pund, E R J Med A Georgia, 26 16 1937
- 8 Rake, G W, Shaffer, M F and Thygeson, P Proc Soc Exper Biol & Med, 43 332-334, 1942
- 9 Findlay, G M Tr Roy Soc Trop Med & Hyg, 27 35, 1933
- 10 Gamna, C Arch per le sc med., 46 31, 1925
- 11 Gamna, C Presse med, 32 404, 1924
- 12 Favre, M Presse méd., 32 651, 1924
- 13 Todd, A T Lancet, 2 700, 1926

- 14 Findlay, G M., Mackenzie, R D and MacCallum, F O Tr Roy Soc. Trop Med & Hyg., 32 183 1938
- 15 Rake, G and Jones, H Proc. Soc Exper Biol. & Med., 53:86 1943
- 15a Lymphogranuloma Venereum, A Monograph. E. R. Squibb & Sons, 1943
- 16 Torpin R., Greenblatt, R. B., Pund E. R and Sanderson, E. S Am J Surg., 43:688 1939
- 17 Grace, A. W Bull New York Acad Med., 17:627, 1941
- 18 Levy, H J Pediat., 11:812 1937
- 19 Dick W Med Klin., 32 319 1936
- 20 Harm A and Mathewson, C. Jr J.A.M.A., 108:961 1937
- 21 Sullon, S E., Fletcher P F., Hubert, E. T and Reb E. R. J.A.M.A., 116 2663, 1941
22. Graham, W E. Ven. Dis. Inform. (Supp 13) U.S Public Health Service, 1941, p 18
- 23 Levaditi C., Mollaret, P and Reine L Bull Acad de méd., Paris, 113 439 1935
- 24 Kirsner J B., Rodaniche, E. C. and Palmer W L. Am. J Digest. Dis., 9 229 1942
- 25 Caminopetros, J Bull soc. path exot., 28:408 1936
26. Levaditi, J C. La Maladie de Nicolas, Favre Experimentale These de Paris, 1936
- 27 Bloom, D New York State J Med., 38:616 1938
- 28 Pub Health Rep., 50 1017 1935
- 29 Lehmann, C. F and Pipkin J L Texas State J Med., 29 192 1933
- 30 Stannus, H S A Sixth Venereal Disease London, Bailliere, Tindall and Cox, 1933
- 31 Bacon, H D and Meharg J G The Medical World 53 705 1935
- 32 Kampmeier R. H and Larsen, H M. Am. J Syph., Gonorr & Ven Dis., 26 316, 1942
- 33 Von Haam, E. and D'Aunoy R Am. J Trop Med., 16 527-546, 1936
- 34 Zarakonets, C. J D New England J Med. 230 567 1944
- 35 Brandt, R. Ven Dis Inform., 22:248, 1941
36. Greenblatt, R. B Ven Dis. Inform., Supp 19
- 37 Stannus H S Brit. Encycl. Med. Practice, Vol VIII pp 287 1938
- 38 Gray L. A. and Barnes, M L. Am. J Surg., 48 277 1940
- 39 Frei, W J.A.M.A., 110 1653 1938
- 40 Grace, A W and Henry G W. New York State J Med., 40 285 1940
- 41 Bensaudé, R., Lambling A et al Proc. Roy Soc. Med., 29 1441 1936
- 42 Palmer W L., Kirsner J B and Rodaniche, E. C. J.A.M.A., 118 517 1942
- 43 Greenblatt, R. B Am. J Surg., 49:411 1940
- 44 Klein I Am J Roent., 51 70 1944
- 45 Longmure, W P Surgery 15:997 1944
46. Pollard W E. and Hellendall, H. Am J Obs. & Gynec., 44 317 1942
- 46a. Bergen, J A. J.A.M.A., 126 1009 1944
- 47 Finn, W F. Am. J Obs. & Gynec., 48:696, 1944
- 47a Coutts, W E. J Urol., 49 595 1943
- 48 Buschke, A., Boss, A. and Von Vasarhelyi J., through Stannus, H S. A Sixth Venereal Disease. London Bailliere, Tindall & Cox, 1933 p 52
- 49 Ravaut, P and Scheikevitch Bull et mém Soc. méd d hôp de Paris, 45 310 1921
- 50 Myerson, M C. J.A.M.A., 117 1877, 1941
- 51 Levaditi, C., Bollock, J., Basch G and Desvignes, P. Bull Soc franç de dermat. et syph., 43 1238, 1936
- 52 Curth W., Curth, O and Sanders, M. J.A.M.A., 115 445 1940
- 53 Klotz, H G Berlin Klin Wchnschr., 27 132, 1890.

- 54 Hellerstrom, S Acta dermat-venereol., Stockholm, 8 394, 1928
- 55 Harrop, G A, Rake, G and Shaffer, M F Tr A Am Physicians, 56 101, 1941
- 56 Chevallier, P and Bernard, J (thru 22)
- 57 Sabin, A B and Aring, C D J A M A., 120 1370, 1942
- 58 Martin, C F Am J Digest. Dis & Nutrition, 2 741, 1936
- 59 Cardwell, E S and Pund, E R J A M A Georgia, 29 60, 1940
- 60 Deibert, A V and Greenblatt, R B Am J Syph., Gon and Ven Dis, 26 330, 1942
- 61 Greenblatt, R B Am J Surg, 49 411, 1940
- 62 Grace, A W and Suskind, F H Proc Soc Exper Biol & Med, 32 171, 1934
- 63 Grace, A W and Suskind, F H Arch Dermat. & Syph, 33 853, 1936
- 64 Grace, A W Arch Dermat & Syph., 39 347, 1939
- 65 Binkley, G W and Love, W R Arch Dermat & Syph., 38 383, 1938
- 66 Strauss, M J and Howard, M E J A M A., 106 517, 1936
- 67 Rake, G., Shaffer, M F, Grace, A W, McKee, C M and Jones, H D Am J Syph, Gonorr & Ven Dis, 25 687, 1941
- 68 Miyagawa, Y, Mitamura, T, Yaoi, H, Ishii, N and Okanishi, J Jap J Exper Med, 13 733, 1935
- 69 Rake, G., McKee, C M and Shaffer, M F Proc Soc Exper Biol & Med., 43 332, 1940
- 70 Greenblatt, R B J Oklahoma M A., 34 423, 1941
- 71 Mortara, F and Greenblatt, R B Ven Dis Inform, 24 14, 1943
- 72 Axelrod, S J Am J Syph, Gonorr & Ven Dis, 26 474, 1942
- 73 Heisel, E. B., Stroud, G., et al Arch Dermat & Syph., 48 379, 1943
- 74 Wolf, J and Sulzberger, M B Brit. J Dermat, 44 192, 1933
- 75 Pund, E. R., Greenblatt, R B and Huie, G B Am J Syph., Gonorr & Ven Dis, 22 495 (July) 1938
- 76 McKee, C M., Rake, G W and Shaffer, M F Proc Soc Exper Biol & Med., 44 410, 1940
- 77 Grace, A W and Rake, G Arch Dermat. & Syph, 48 619, 1943
- 78 Nigg, C and Bowser, B M Proc Soc Exper Biol & Med, 53 192, 1943
- 79 Francis, T., Jr and Magill, I P J Exper Med, 68 147, 1938
- 80 Eaton, M D., Martin, W P and Beck, M D J Exper Med, 75 21, 1942
- 81 Rake, G W, Eaton, M D and Shaffer, M F Proc Soc Exper Biol & Med, 48 528, 1941
- 82 Frei, W J Invest Dermat, 2 119, 1939
- 83 Gutman, A B New York State J Med, 39 1420, 1939
- 84 Kampmeier, R H, Smuth, D W and Larsen, R M Am J M Sci, 198 516, 1939
- 85 Gutman, A B and Wise, C R Proc Soc Exp Biol & Med, 35 124, 1936
- 86 Tasaki, K J Orient. Med, 24 805, 1936
- 87 Wise, C R and Gutman, A B Am J Med Sc, 194 263, 1937
- 88 Howard, M E., Eisenman, A J and Strauss, M J Am J Syph, Gonorr & Ven Dis., 23 83, 1939
- 89 Rosen, I., Rosenfeld, H., Bloom, D and Krasnow, F Arch Dermat. & Syph., 39 211, 1939
- 90 Kroll, M M and Cohart, E. M Am J Syph, Gonorr & Ven Dis, 28 320, 1944
- 91 Brandt, R and Torpin, R Am J Syph, Gonorr & Ven Dis, 24 632, 1940
- 92 Knott, L W., Bernstein, L H T., Eagle, H et al Am J Syph, Gonorr & Ven Dis, 24 632, 1940
- 93 Gelperin, A Am J Syph, Gonorr & Ven Dis., 27 697, 1943

- 94 Greenblatt, R. B. and Wright, J. C. *Am. J. Syph., Gonorr & Ven. Dis.* 20 654, 1936
- 95 Stroog R. P. *Stutt's Diagnosis, Prevention and Treatment of Tropical Diseases*, 6th ed., 1943, Vol. 2, p. 1325
- 96 Glauser F. *U. S. Nav. M. Bull.*, 44 21 1945
- 97 Strong, R. B. *Stutt's Diagnosis, Prevention and Treatment of Tropical Diseases*, 6th ed., 1943 Vol. 2 p. 1412
- 98 Pasternack J. G. *J.A.M.A.*, 112 1814 1939
- 99 Brandt, R. and Greenblatt, R. B. *Southern M. J.*, 34 941 1941
- 100 Stokes, J. H., Beerman, H. and Ingraham, N. R., Jr. *Am. J. M. Sc.*, 197 575 1939
- 101 Jones, H. P., Rake, G. and McKee, C. M. *Proc. Soc. Exper. Biol. & Med.*, 48 318 1941
- 102 Grace, A. W. *J.A.M.A.*, 122 74 1943
- 103 Marshall, E. K., Jr., Bratton A. C., White, H. J. and Litchfield J. T., Jr. *Bull. Johns Hopkins Hosp.*, 67 163, 1940
- 104 Levy J. G., Holder E. C. and Bullock J. G. M. *Am. J. Digest. Dis.*, 9 237 1942
- 105 Oliphant, J. W., Powell, W. F. and Perrin, T. L. *J.A.M.A.*, 118-973, 1942
- 106 Seeler A. O., Graessle O. E. and Dusenbery E. D. *J. Bact.*, 45 205 1943
- 107 Callomon, F. T. and Brown, H. *Am. J. Syph., Gonorr & Ven. Dis.*, 27 490 1943
- 108 Rodaniche, E. C. *J. Infect. Dis.*, 73 173 1943
- 109 Wien, M. S. and Perlstein, M. D. *Brit. J. Dermat.*, 49 63 1938
- 110 Bercovitz, A. M. *Clin. North America*, 24 683, 1940
- 111 Gay Prieto J. *Dermat. Wechschr.*, 95 1056 1932.
- 112 Anderson, O. L. and Harnos, O. *Surgery* 3 41 1938
- 113 Kornblith, B. A. *Am. J. Med. Sc.*, 198 231 1939
- 114 deGregorio E. *Ann. d. mal. vén.*, 32 413 1937
- 115 Hellerstrom, S. *Acta dermat. venereol.*, 17 283 1936
- 116 Greenblatt, R. B. and Brandt R. *Am. J. Syph., Gonorr & Ven. Dis.*, 25 75 1941
- 117 Costello M. J. and Cohen, J. A. *Arch. Dermat. & Syph.*, 44 391, 1941
- 118 Prats, G. F. *Am. J. Syph., Gonorr & Ven. Dis.*, 24 799 1940
- 119 Katz, F. and Sagher F. *Dermat. Wechschr.*, 92 1754 1933
- 120 DeWolf, H. F. and Van Cleve, J. F. *J.A.M.A.*, 99 1065 1932



# PENICILLIN-RESISTANT GONORRHEA

CAPTAIN RICHARD L SAUNDERS AND CAPTAIN MURRAY M MAY  
MEDICAL CORPS, ARMY OF THE UNITED STATES

In the spring of 1944, at Hammond General Hospital, 212 consecutive cases of sulfonamide-resistant gonorrhea in the male were treated with intramuscular injections of penicillin. Of this number, seventeen patients or 8 per cent were not benefited by the penicillin treatment. As other reports dealing with penicillin therapy in the treatment of uncomplicated gonorrhea in the male state that 98 to 100 per cent cures are obtained,<sup>1,2</sup> the failure of penicillin therapy in 8 per cent of the patients in this series is unusual and requires careful analysis. No reports dealing specifically with failure of penicillin therapy in the management of gonorrheal infections have appeared in the literature to date.

TABLE 1—THE AMOUNT IN UNITS AND NUMBER OF COURSES OF PENICILLIN ADMINISTERED TO THE ENTIRE SERIES OF 212 PATIENTS, IN RELATION TO THE FAILURES OF THERAPY

No Cases	1st Course	2nd Course	3rd Course	Total per Patient	No Failures
106	50,000			50,000	0
15	50,000	100,000		150,000	0
9	50,000	100,000	200,000	350,000	5
1	50,000	200,000	800,000	1,050,000	1
47	100,000			100,000	0
15	100,000	100,000	200,000	400,000	9
17	100,000	100,000		200,000	0
1	100,000	100,000	100,000	300,000	1
1	100,000	100,000	300,000	500,000	1
212					17

The first course of treatment in the 212 cases was administered according to Army directive.<sup>3</sup> In all of the seventeen cases listed as failures the patients received three courses of treatment with penicillin before failure of therapy was considered to be established (Table 1). Although the criteria of cure in the 92 per cent in whom penicillin was adjudged effective may be subject to some question, the evidence of failure in the 8 per cent is obvious.

## ANALYSIS OF CASES IN WHICH A CURE WAS OBTAINED

All injections of penicillin in this series were given by the intramuscular route at three-hour intervals. An analysis of the 195 cases which

met the criteria of cure is given in detail in Table 2. One hundred and twenty-five patients were treated with an original course of 50,000 units in doses of 10,000 units every three hours. One hundred and six of these or 85 per cent were cured with a single course. A second course of 100,000 units added 12 per cent additional cures. A third course yielded 3 per cent additional cures.

Seventy patients were treated with an original course of 100,000 units given in doses of 20,000 units every three hours. Forty-seven of these or 67 per cent were cured with a single course. A second course of 100,000 units added 24 per cent additional cures. A third course resulted in 9 per cent additional cures.

**Criteria of Cure**—Using an Army directive dated September 23, 1943<sup>8</sup> as a basis, the following regimen and criteria of cure were adopted. If there was no evidence of discharge for three days after

TABLE 2—THE AMOUNT IN UNITS AND NUMBER OF COURSES OF PENICILLIN USED IN 195 PATIENTS WHO WERE CONSIDERED CURED, AND THE PERCENTAGE OF CURES FROM ONE COURSE OF TREATMENT AND THE PERCENTAGE OF ADDITIONAL CURES FROM EACH SUBSEQUENT COURSE

No. Cases	1st Course	2nd Course	3rd Course	Total per Patient	Per Cent Cured
106	50,000			50,000	85
15	50,000	100,000		150,000	12
4	50,000	100,000	200,000	350,000	3
<u>125</u>					<u>100</u>
47	100,000			100,000	67
17	100,000	100,000		200,000	24
6	100,000	100,000	200,000	400,000	9
<u>70</u>					<u>100</u>

treatment, freedom from infection was assumed. If discharge persisted or recurred by the second day, smears and cultures of the discharge were made. If these were negative the patient was also assumed to be free of infection. In cases of persistent discharge and positive smears, further penicillin treatment was instituted. From the beginning of this study it was decided to insist on a negative culture either from urethral discharge, from urine, or from prostatic secretion before disposition of the patient was made. This culture was taken at least forty-eight hours after treatment was completed.

It is obvious that such a short follow-up of the effectiveness of therapy by penicillin injections is unsatisfactory statistically but it was not practical to retain a large number of patients in the hospital for follow-up observations as it may be assumed that the majority of cases would remain smear and culture negative. However, the work of Koch and his associates showing a relapse rate of 32 per cent in

three months,<sup>4</sup> reveals the importance of follow-up cultures, and indicates that the percentage of failures in this series would be increased beyond 8 per cent if a prolonged follow-up of our patients had been possible

#### ANALYSIS OF FAILURES

An analysis of the seventeen patients in whom penicillin therapy was ineffective reveals that repeated courses of treatment with large doses of penicillin were of no avail in this group (Table 3). It should again be emphasized that each patient in this group of therapeutic failures was treated with three courses of penicillin. One patient received a total of 300,000 units, five patients received 350,000 units, nine patients received 400,000 units, and one patient received 500,000 units. One additional patient was given a total of 1,050,000 units, 800,000 units being given during the third course, without beneficial effect. It is noteworthy that the same three-hour interval between doses was used in all courses of treatment and that the maximum single dose given in

TABLE 3 —THE AMOUNT OF PENICILLIN IN UNITS EMPLOYED IN THE TREATMENT OF SEVENTEEN PATIENTS IN WHOM PENICILLIN THERAPY WAS INEFFECTIVE

No. Cases	1st Course	2nd Course	3rd Course	Total per Patient
5	50,000	100,000	200,000	350,000
1	50,000	200,000	800,000	1,050,000
9	100,000	100,000	200,000	400,000
1	100,000	100,000	100,000	300,000
1	100,000	100,000	300,000	500,000
17				

any case was 20,000 units. In those patients receiving more than 100,000 units during a course of treatment, the duration of the treatment period was extended beyond the usual fifteen hours until the total dosage was accomplished. For example, the one patient who received 800,000 units during the third course of treatment (Table 3), was given 20,000 units every three hours for 120 hours.

In this group of seventeen failures, there were seven patients whose cases were considered to be new, in that the history indicated that infection had been present less than six months. The other ten cases were designated as chronic in that symptoms had existed for more than six months.

**Possible Causes of Failure** —The reason for the failure of penicillin to eradicate infection with the gonococcus in this group of cases remains unexplained. The possibility that some technical difficulty was responsible was explored. However, it was obvious that cures were being effected at the same time that the failures in therapy were occurring.

Changing the brand of penicillin that was being used to another brand manufactured by a different pharmaceutical firm did not alter the percentage of failures. The potency of the penicillin against the Oxford strain of staphylococcus was tested. This strain was found sensitive in a dilution of 0.03 units per cubic centimeter, indicating that the penicillin was of satisfactory potency. Blood levels of penicillin were determined in two cases classified as failures (Table 4). This concentration was within a satisfactory therapeutic range. Tests also indicated that there was no difference in the potency of the penicillin in distilled water from that in saline.

That failure in therapy might be a biological one was also considered. The significant possibility that certain strains of gonococcus might be or become penicillin resistant was recognized, but sensitivity tests *in vitro* to determine whether penicillin resistance could account for our adverse findings could not be carried out in the hospital laboratory. Relative to this problem, a communication from Major Ayer, Chief of Laboratory Service of the O'Reilly General Hospital, Springfield, Missouri, on March 28, 1944, stated that "Penicillin sensitivity tests during

TABLE 4—THE PENICILLIN BLOOD LEVELS IN TWO PATIENTS IN WHOM PENICILLIN FAILED TO CLEAR UP GONOCOCCUS INFECTION, THE TITER IS WELL WITHIN THE EFFECTIVE RANGE

CASE I	1.25 units/cc. one-half hour after second dose of 20,000 units
	0.078 units/cc. one and one-half hours after second dose of 20,000 units
CASE II	0.62 units/cc. one-half hour after second dose of 20,000 units
	0.078 units/cc. one and one-half hours after second dose of 20,000 units

the past four months have not disclosed any strain of *N. gonorrhoea* that was initially or has become resistant to the therapeutic agent. The organisms fell invariably within a range of 0.005 to 0.05 units per cc. for complete inhibition. This is true even for organisms isolated from patients who were not cured after receiving 100,000 units." Recent publications on the elaboration of antipenicillin substance by certain bacteria do not include the gonococcus except in one instance. This substance has been termed penicillinase by certain writers and one strain of gonococcus has been reported as negative for the production of penicillinase.<sup>5</sup> To date, positive evidence is lacking that certain strains of the gonococcus are resistant to penicillin.

#### MANAGEMENT OF THE PENICILLIN RESISTANT CASES

The treatment of seventeen penicillin-fast patients proved an interesting though difficult problem. One patient who had received 400,000 units was subsequently cured with *sulfathiazole*. This patient was the only one in the series who had not previously received sulfonamide therapy. He was included in the series in order to emphasize the fact that in some instances sulfonamides may be effective even though

penicillin has previously failed. One patient was cured after a *meatotomy* was performed and urethral irrigations with potassium permanganate, 1 10,000 solution were administered. One patient had a marked diverticulum of the urethra. Surgery was not considered advisable and he was given a course of potassium permanganate irrigations which proved ineffective. This patient was discharged to a Veteran's Facility and it was not possible to follow his ultimate course. The remaining fourteen cases were referred to the genito-urinary section of the Surgical Service for *fever therapy*. The average duration of the therapeutic fever was fourteen hours during which time the fever was maintained between 104° and 106° F. The general plan of treatment for these patients was as follows:

If no urethral discharge was noted after the fever therapy, no further treatment was given. Five days after fever therapy or after cessation of the discharge, cultures from the prostatic secretion were made. After three consecutive negative cultures made at approximately forty-eight-hour intervals, the patient was pronounced cured. If urethral discharge persisted, the patient was given daily irrigations of *potassium permanganate solution* and *prostatic massage* twice daily. This treatment was continued until the discharge had ceased and three successive prostatic smears were negative. If there was no cessation of the discharge after irrigations, the urethra was examined for obstruction.

In four patients the urethral discharge ceased within a few days after fever therapy was started and irrigations were not given. In these cases, prostate cultures were taken within the first ten days following fever, and, after three negative cultures, the cases were pronounced as cured. All four of these patients were returned to duty. In this group the cure can be directly attributed to the fever therapy.

Following fever therapy, four patients continued to have urethral discharge which was negative for gonococci. Urethral irrigations and prostatic massage were continued until the cessation of the discharge. The average period of this treatment in these patients was one month. Subsequent prostatic cultures were negative. Three of these patients were returned to duty and one was given a medical discharge because of a psychiatric diagnosis. Fever therapy probably contributed to the eventual cure of this group of patients.

Four patients continued to have a urethral discharge which was positive for gonococci. This discharge continued for about a month after the last bout of fever. During this time urethral irrigations and prostatic massages were carried out. Upon cessation of the discharge, prostatic cultures were taken. When these were negative, the cases were pronounced cured. Two were returned to duty, and two were discharged from the Army because of psychiatric diagnoses. These four cases were classed as definite failures from fever therapy.

Two additional patients were not cured by either fever therapy or

irrigations. They continued to have a profuse urethral discharge which was positive for gonococci. Repeated prostatic and urine cultures were also positive. One of these patients had a severe urethral stricture and was finally discharged from the Army for this reason. The other patient was transferred to another hospital and follow-up inquiry disclosed that five months after fever therapy the urethral discharge ceased and prostatic cultures were negative without benefit of further treatment.

#### DISCUSSION

The problem of why 8 per cent of these cases of gonorrheal infection failed to respond to penicillin therapy remains unsolved. Also why treatment of 125 cases with a single total course of 50,000 units of penicillin produced cures in 85 per cent while a single course of 100,000 units in seventy cases produced cures in only 67 per cent is difficult to explain. It seems probable that different strains of the gonococcus may vary in their susceptibility to therapy and that cures will not be so readily obtained in any series of cases which may contain a large number of the more resistant strains. Clear-cut biological evidence of this explanation is lacking at present.

Three of the seventeen patients classified as failures on penicillin therapy were discharged from the hospital as not cured, although one of these patients was ultimately reported from another hospital as free of discharge and culture negative. The effect of fever therapy in fourteen patients in this group is difficult to evaluate because other therapeutic procedures were carried out in all but four cases and because there was no prolonged follow-up study of any of the cases to determine whether the patients remained "cured" symptomatically and bacteriologically. For the period of observation, the four patients who received fever only were apparently cured, while two patients were not cured as they remained smear and culture positive. Although eight other patients became bacteriologically negative these negative tests were obtained while the patients were receiving irrigations and can scarcely be accepted as final proof of cure. Nevertheless patients with gonorrhea which do not respond satisfactorily to therapy by sulfonamides and penicillin should have a trial of fever therapy.

One other factor seems to be of importance in treating these patients and that is adequate drainage of the urinary tract. Three of the "failure" patients had obstructive lesions. These were (1) a small meatus for which meatotomy was performed, (2) a marked diverticulum of the urethra and (3) a severe urethral stricture. That this type of case with mechanical obstruction of the urethra may not respond to penicillin therapy unless the obstruction is removed, is borne out by the history of a case recently observed and not included in the original series. This patient had been treated unsuccessfully with sulfadiazine and with penicillin. The dose of penicillin used was initially 20,000 units and then 10,000 units every three hours for eighteen doses.

for a total dosage of 200,000 units. Because the patient had a narrow urethral meatus and marked phimosis, a meatotomy and circumcision were performed. Penicillin therapy was started twelve hours pre-operatively in a dose of 20,000 units every three hours and was continued for seventy-five hours to complete a total dosage of 500,000 units. The discharge cleared up on the fourth day after treatment was started and on the seventh day smears and culture were negative.

#### SUMMARY AND CONCLUSION

1 In a series of 212 patients with sulfonamide-fast gonorrhea treated with penicillin, seventeen failures (8 per cent) occurred.

2 The possible cause of the high percentage of failures in this series is unknown.

3 The management of these patients with penicillin-fast gonorrhea is discussed.

4 A certain number of patients with gonorrhea may not be cured by either sulfonamides or penicillin therapy. Failure of cure by repeated courses of penicillin therapy in seventeen of 212 cases, or 8 per cent, is a higher incidence of failure than previously reported. Some of the patients who were not cured by chemotherapy were apparently cured subsequently by fever therapy and by operation to relieve urethral obstruction.

#### BIBLIOGRAPHY

- 1 Murphy, Robert J., Captain, A U S Experimental Use of Penicillin in Treatment of Sulfonamide Resistant Gonorrhea. Bull U S Army Med Dept., 79 101, 1944.
- 2 Robinson, J N Penicillin. Brit. M J, 2 655 (Nov 20) 1943, Lancet, 2 639 (Nov 20) 1943, J.A.M.A., 124 117, 1944.
- 3 Headquarters, 9th Service Command, September 23, 1943.
- 4 Koch, R., Mathis, E and Geiger, J Vener Dis Inform., 25 35, 1944.
- 5 Bondi, Amedeo and Dietz, Catherine C Proc Soc Exper Biol & Med., 50 132, 1944.

## ACUTE ACQUIRED HEMOLYTIC ANEMIA

LT COLONEL GARNETT CHENEY AND MAJOR EDWARD J DENENHOLZ  
MEDICAL CORPS, ARMY OF THE UNITED STATES

It has been pointed out that acute hemolytic anemia may develop as a result of a variety of etiologic agents, such as hemolysins of the immune body type, agglutinins, chemicals, bacteria and other infectious agents.<sup>1</sup> This clinical picture may also occur as a manifestation of an underlying systemic disorder such as Hodgkin's disease or leukemia, and to this latter type the term "symptomatic hemolytic anemia" has been applied.<sup>2</sup> In the recent literature, considerable attention has been directed to acute hemolytic anemia following administration of sulfonamide drugs,<sup>3</sup> following the development of anti-Rh agglutinins in the newborn,<sup>4</sup> and in Rh-negative individuals during pregnancy or after repeated transfusions<sup>5</sup> and occurring in association with cold hemagglutinins.<sup>6</sup> In addition to these groups, however, there is a type of acute hemolytic anemia which develops in a previously healthy individual and for which no etiology can be determined. These cases have been termed "acquired hemolytic icterus," "acute hemolytic anemia," "acquired hemolytic anemia,"<sup>8</sup> and the Hayem-Widal type of hemolytic anemia.<sup>7</sup> In some of these patients antibodies of an immune body type<sup>9</sup> may be detected, but in the majority no such serologic findings are present. A patient with acute acquired hemolytic anemia of unknown etiology observed at Hammond General Hospital, presented some of the characteristic features of this condition, but also demonstrated several rather unusual aspects of the disease, and its treatment.

### REPORT OF THE CASE

**History**—This 24 year old white male with two and one half years of military service was admitted to Hammond General Hospital April 25 1944 by transfer from a station hospital. He stated that he had "never been ill" and had always been unusually healthy. It was later learned that he was the outstanding athlete at his post. About three months before entry to the hospital he noted that, following vigorous athletic activities, he became fatigued more readily than usual. Early in April following a basketball game, he developed nausea, headache, dizziness and weakness, lasting for several hours. The following day a medical officer who passed him in the corridor noted his pallor and suggested that a blood count be made. This revealed red blood cells 2 100 000; hemoglobin 45 per cent; leukocytes 11,650 with 62 per cent polymorphonuclears. The patient was admitted to the station hospital where during the course of the next ten days he received three blood transfusions of 500 cc. each. The red blood cell count following his third transfusion was 1 860 000 and hemoglobin 40 per cent, and for this reason he was transferred to a general hospital. There was no history of exposure to or ingestion of drugs. There was no history of a similar illness in any other member of the family.



**Physical Examination**—The patient appeared toxic and acutely ill and presented marked pallor with slight icteric tinge to the skin and mucous membranes. The temperature was 102° F, pulse 110 and respirations 28. The cheeks were flushed and the vessels in the neck were pulsating. There were no purpura or petechiae. There was a soft systolic murmur over the third interspace to the left of the sternum, which was interpreted as being hemic in origin. The liver and spleen were palpable at the costal margin. No adenopathy was present.

**Laboratory Findings**—Initial *blood studies* showed red blood cells 1,440,000, hemoglobin 27 per cent, leukocytes 24,550 with 65 per cent polymorphonuclears and 29 per cent lymphocytes. There were 26 nucleated red cells per 100 white cells and 54 per cent reticulocytes. The platelet count was 120,000. The stained smear showed a moderate number of small dense cells, large slate-gray cells and many small nucleated red cells with dense pyknotic nuclei. There was marked polychromatophilia and basophilic stippling. Hematocrit was 15 per cent, volume index 1.13 and average red cell diameter was 7.5 microns by the halometer method. The fragility test showed initial hemolysis beginning at 0.60 and complete at 0.44. The icteric index was 50. The serum proteins were 11.2 gm, albumin 5.5 gm and globulin 5.7 gm per 100 cc. The urine was negative for bile, positive for hemoglobin and positive for urobilinogen in a dilution of 1:50. The blood group was O, and the patient was Rh-positive. Neither hemolysins nor agglutinins could be demonstrated. Blood studies on the patient's two sisters including blood count, fragility test and icteric index yielded normal findings.

**X-rays** of the chest, skull and long bones were negative.

**Management and Course**—The patient was given 500 cc of citrated blood from a Group O donor after careful compatibility tests at ice box, room and incubator temperatures. Despite this, the following day the blood count was essentially unchanged, and he appeared worse. The urine was deep reddish-purple in color, showed only a few red cells and was markedly positive for hemoglobin. Inasmuch as the patient had had four blood transfusions with no apparent improvement, and hemolysis was continuing, it was felt that a splenectomy was urgently indicated. Under spinal anesthesia, splenectomy was performed twenty-four hours after the patient entered this hospital. The operation was well tolerated and for a few days the patient appeared to be progressing fairly well. However, on the fourth postoperative day, the temperature rose to 104° F and the red cell count dropped to 1,020,000 with 26 per cent hemoglobin. There were 16,500 leukocytes per cubic millimeter and 23 per cent reticulocytes. It was recognized at this time that in view of the continuing hemolysis following splenectomy, the prognosis was poor. However, it was felt that there was no recourse other than a continuation of blood transfusions when the blood counts reached extremely low levels. Intramuscular injections of crude liver extract were started, and a transfusion of 500 cc of citrated blood was given. Sodium bicarbonate, 12 gm by mouth daily, was also begun to prevent the formation of acid hematin in the kidneys.

On the seventh postoperative day the red cell count had dropped to 860,000 with 24 per cent hemoglobin. The leukocyte count was 9000 and there were 130 nucleated red cells per 100 white cells and 11 per cent reticulocytes. The patient failed to develop postoperative thrombocytosis, the highest platelet count, 125,000 per cubic millimeter, being present on this date. A transfusion of 500 cc of whole blood was followed by a chill, fever of 105° F and reappearance of gross hemoglobinuria. At this time penicillin therapy, 50,000 units intramuscularly every three hours, was instituted, and continued for nine days until a total dose of 2,500,000 units was attained. There was no demonstrable beneficial effect. Fever continued to range to a peak of between 103° and 104° F daily. Repeated blood counts indicated little change. The serum protein at this time was 14 gm.

per 100 cc., which was attributed to the tremendous red cell destruction and the failure of the liver to convert and excrete the bilirubin protein complex. Generalized hyperesthesia with marked muscle tenderness was an outstanding feature. Gastrointestinal complaints anorexia and abdominal pain were also prominent. On the tenth postoperative day the patient was given 500 cc. of whole blood which was again followed by a similar severe reaction.

On the twelfth hospital day after satisfactory cross matching the patient was given 1000 cc of washed resuspended Group O red cells with no reaction (obtained from the blood donor center San Francisco, Red Cross Chapter). However within forty-eight hours the red cell count and hemoglobin had dropped to the pretransfusion level. This procedure was repeated at intervals of every two or three days, as indicated by the red cell count and the clinical course, although when the fourth washed red cell transfusion was given on the nineteenth hospital day the patient developed a severe chill and a temperature rise to 104.8 F. The following day however the red blood count was the highest that it had been since his entry to the hospital red blood cells 2,840,000, hemoglobin 50 per cent, leukocytes 15,600 with 82 per cent polymorphonuclears. There were 122 nucleated red cells per 100 white cells and the reticulocytes had decreased to 4.1 per cent. The leukocytes showed evidences of toxic changes with only a few young forms being present. Bone marrow biopsy done this day showed no evidence of leukemia or Hodgkin's disease.

Subsequent to this the patient's course was rapidly downhill. He developed edema, pain and coldness of the right leg and foot, and it was thought that a venous thrombosis was present. The temperature continued ranging to peaks of 103 to 104 F almost daily accompanied by generalized abdominal pain, marked anorexia and vomiting. Subsequently he was given washed red cell transfusions at intervals of two to five days. Following each of these, he developed a chill and a rise in temperature to 104 or 105 F. However, the relationship of the temperature rise to the administration of the blood cells was difficult to evaluate inasmuch as the patient had exhibited a high fever almost daily.

Hemoglobinuria disappeared although albumin, hyaline and granular casts and red cells appeared in the urine. The urine was positive for urobilinogen in a dilution of 1:50. Repeated fragility tests showed hemolysis beginning at 0.66 to 0.64 and complete at 0.48 to 0.44. Repeated examinations failed to show the presence of iso- or autoagglutinins or hemolysins. The striking evidence of bone marrow activity continued in the blood smears, so that on the twenty-fifth postoperative day there were 169 nucleated red blood cells per 100 white cells. On the thirty-first hospital day the patient developed chest pain, raised scanty blood stained sputum and developed increasing weakness, and dyspnea. Dullness, crepitant rales and diminished breath sounds were found over both lower lobes. An x-ray of the chest showed clouding of both lower lung fields.

On the day before the patient's death the blood count was red blood cells 1,590,000 hemoglobin 39 per cent, leukocytes 39,630 72 per cent being polymorphonuclears with 2 per cent young forms and 26 per cent lymphocytes. There were 7 cells per 100 white cells and reticulocytes were 4.9 per cent. The icteric index was 22. He lapsed into a coma and died on the thirty-fifth hospital day.

**Pathologic Examination (Major Russell Kerr)—Spleen (Surgical Specimen)**—The spleen measured 15 by 10 by 7 cm. on section the pulp was deep purplish in color, the trabeculae were discernible though the malpighian bodies were not distinct. Histologic section revealed marked congestion of the sinusoids, and wide separation of the malpighian bodies. Large phagocytic cells containing blood pigment were noted in the pulp and nucleated red cells were present in the sinusoids.

**Bone Marrow (Biopsy)**—Histologic examination revealed marked cellularity

of the marrow with the predominant increase being in erythroblastic cells. Many of the cells were nucleated red cells and megalocytes. Moderate activity of the myeloid cells was present but there was no evidence of "maturation arrest."

*Autopsy*—The pertinent findings were a thrombus in the distal portion of the splenic artery, multiple pulmonary thrombi with infarction, bilateral hydrothorax and hyperplasia of the bone marrow. Microscopic examination showed extensive hemorrhage throughout the lungs with complete infarction throughout some areas and the presence of obliterating thrombi in many of the medium-sized pulmonary vessels. The liver showed marked distortion of the architecture, distention of the sinusoids, hemosiderosis and in many of the sections there was actual necrosis of the liver cells. Sections through the kidneys showed mild parenchymatous changes in the convoluted tubules. Bone marrow sections corroborated the findings obtained previously at biopsy.

#### COMMENT

This patient was of unusual interest for a number of reasons. The occurrence of acute hemolytic anemia in a previously healthy individual in the military service is indeed rare. This is the first case of this type that has been encountered in approximately 11,000 admissions to this hospital, though two patients with chronic hemolytic anemia of the familial type and one patient with symptomatic hemolytic anemia have been observed. This latter patient was found to have an undifferentiated malignant tumor as the underlying basis of the hemolytic anemia. The presence of marked hemoglobinuria in this condition is likewise worthy of mention. Mason did not observe hemoglobinuria in any of the patients in his series,<sup>6</sup> nor did Damashek and Schwartz.<sup>10</sup>

The problem of diagnosis was also of considerable interest. The patient was transferred to this hospital with the diagnosis of congenital hemolytic anemia. It was felt, however, that the absence of any history of anemia or jaundice in earlier life, the absence of a familial history of the disease together with the normal blood findings in other members of the family and the clinical picture of the illness militated against this diagnosis. No etiologic factor for the hemolytic anemia could be determined and in view of this and because of the characteristic blood findings, a diagnosis of acquired hemolytic anemia of unknown etiology was ventured. Briefly it may be stated that little is known concerning the cause and method by which hemolysis occurs in the patients. A discussion of the theories of pathogenesis, and mechanism of hemolysis in this condition are beyond the scope of this clinical report. Comprehensive presentations of these aspects and reviews of recent experimental work in this and allied disorders have recently appeared in the literature.<sup>3, 6, 8, 9</sup>

The number of nucleated red cells of the normoblastic type noted in the stained blood smears was striking throughout the period of observation. The number ranged, as demonstrated on daily blood counts, from 26 per 100 leukocytes on the day of entry to this hospital to 169 per 100 leukocytes on the twenty-fifth postoperative day. Following this, evidence of bone marrow activity decreased rather markedly so

that for a week before exodus there were only 7 to 15 nucleated cells per 100 white blood cells. There was no correlation between the number of nucleated red cells and the severity of the anemia, the administration of blood transfusions or the clinical condition of the patient, except during the last week of life as noted. Spherocytes, on the other hand, though present were not a prominent feature in this patient at any time.

The use of penicillin was of particular interest and was felt justifiable since this disease in many respects presents the characteristics of an acute infection and since following splenectomy it appeared almost certain that the patient would succumb. Penicillin had no beneficial effect.

The employment of washed resuspended red cells instead of whole blood would seem to offer several advantages. The red cells suspended in saline are Group O cells, and contain no agglutinin. The agglutinins a and b which are present in the serum of Group O individuals, and may be a cause of reactions, need not be considered since the cells are suspended in saline and free of these agglutinins. Hyperproteinemia, such as was present in this patient, may be increased materially by the use of whole blood but not by washed red cells. On the other hand, it has been pointed out that stored cells may be more fragile and that serum may have some antihemolytic property. The appearance of severe reactions in this patient following transfusion of washed red cells is difficult to explain, particularly since the reactions occurred only after the fourth transfusion of washed cells. This suggests the development of some isosensitization, either with agglutinins or hemolysins though none could be demonstrated. Rh agglutinins did not require consideration since the patient was Rh positive. The histologic findings of the bone marrow biopsy and of the spleen were typical of this condition, as were the autopsy findings, including thrombosis and infarction of the lung.

#### CLINICAL PICTURE

The symptoms are dependent upon rapid destruction of blood and resemble an acute febrile illness with toxemia, progressive anemia and jaundice. The onset is usually acute in the course of a few weeks, or may be fulminating, the symptoms developing in less than a week. Mason<sup>6</sup> feels that a careful history often reveals that the symptoms begin insidiously a few weeks to a few months before the patient consults a physician. Common early symptoms are weakness, generalized aching, dizziness, faintness on exertion and gastrointestinal symptoms such as anorexia, abdominal pain and vomiting. These symptoms are soon followed by those of anemia, anoxemia and jaundice. Fever is almost invariably present, may range from 101° to 105° F and is often accompanied by chills. If hemolysis is marked, prostrating shock may occur and hemoglobin appears unchanged in

The urine and stools are both dark though anuria or oliguria may develop

Physical examination reveals an acutely ill, toxic patient with fever, moderate to marked pallor and mild icterus. The veins in the neck are often seen to throb, there is a hemic murmur over the precordium and tachycardia is marked. In about one third of the cases the liver is moderately enlarged, and in about one half the spleen is palpable, though the enlargement is not marked. Venous thromboses of the extremities and infarcts in the spleen, lungs and nervous system are not unusual. The duration varies considerably and often is dependent upon treatment, though spontaneous remissions occur. Some cases respond to one or more transfusions, some to splenectomy, and in others the hemolytic process continues despite therapy. Mason has directed attention to a subacute or chronic form which may develop following acute hemolytic anemia, even after splenectomy, and he feels that this form is more common than the acute type.

**Blood**—The anemia is profound, and may be normocytic or macrocytic. The red cell destruction may be so great that drops in the red cell count of as much as 1,000,000 cells may occur in twenty-four hours and the red cell count fall to less than 1,000,000 cells per cubic millimeter. The stained smear shows a striking variation between small dense cells and large slate-gray red cells. The small cells are spherocytes or microcytes, which Mason<sup>6</sup> terms "microspherocytes." The large cells are reticulocytes, and for this reason have been termed "pseudomacrocytes" by Damashek and Schwartz.<sup>10</sup> In spite of the severe anemia, there is evidence of intense activity of the bone marrow in both the red and white cell series. Reticulocytosis may rise to 50 to 80 per cent and polychromatophilia with many nucleated red cells may appear. These normoblastic cells may reach extraordinarily high numbers in the blood, as in this patient. Leukocytosis, with a shift to the left, is also a characteristic feature. The platelet count is usually normal.

Increased fragility of red cells in this disorder was first described by Chauffard in 1907.<sup>8</sup> In the majority of cases, however, the fragility test is normal though decreased resistance to hypotonic saline may occur. Among twelve patients reported by Mason the fragility test was normal in eight, and showed increased fragility in four. Some patients may show a wide range in the span of the fragility test.

Demonstrable hemolysins and agglutinins occur only infrequently in this disorder, though autoagglutinins and hemolysins were reported as early as 1908 by French clinicians. Mason was unable to observe hemolysins in any of his twelve patients though autoagglutinins were found in four patients. The significance of these antibodies and their importance in the pathogenesis of the disease is still a moot question, some recent articles emphasizing that these antibodies may result from

\* excessive blood destruction rather than act as a causative agent.<sup>11</sup>

It must be pointed out that the failure to demonstrate these antibodies *in vitro* does not preclude their presence.

As a result of the inability of the liver to handle the increased amount of bilirubin which occurs as a result of the red cell destruction, the bilirubin level of the blood is elevated, the blood serum reveals a high icteric index and the van der Bergh reaction yields a positive indirect result. Serum protein values may be elevated, as in this patient.

**Urine**—These findings are also dependent on the degree of the hemolysis. Bile is not present in the urine but urobilinogen is markedly increased. When the hemolysis is extreme, hemoglobin appears in the urine unchanged. Hemoglobinuria in this disorder is rare in adults,<sup>6 10</sup> although is more frequent in children as noted by Atkinson.<sup>12</sup> Mason<sup>6</sup> feels that this may indicate that in this disease the red cells are destroyed in the spleen after being injured in the blood stream, and only when the liver and spleen are overwhelmed does free hemoglobin enter the blood stream. The urine may also contain albumin, granular and cellular casts. Bilirubinuria develops only in the presence of severe liver damage.

**Stools**—Urobilinogen in the stools is greatly increased and the diagnostic importance of this has recently been emphasized. Some observers consider that this is a far better diagnostic test than the presence of increased urobilinogen in the urine, and that it is the most important and most direct evidence of increased hemolysis.<sup>13</sup>

**Bone Marrow**.—Biopsy or bone marrow punch reveals marked evidence of hyperplasia, particularly of the erythroblastic cells. Instead of the normal 20 per cent or less, as many as 60 per cent of the cells may be of the normoblastic series. The similarity to megaloblastic marrow of pernicious anemia is superficial and in acquired hemolytic anemia there is no "arrest level" at the megaloblastic stage.

**Pathology**—In addition to bone marrow hyperplasia, there is usually moderate enlargement of the spleen with congestion of splenic pulp by red cells, multiple areas of thrombosis and infarction, and erythrophagocytosis by giant cells. Enlargement and hemosiderosis of the liver is often present. Necrosis of liver cells such as was present in this patient has been noted.<sup>6 14</sup>

## DIAGNOSIS

The diagnosis of this disease is usually made by exclusion. The sudden onset of profound anemia, icterus, toxemia and fever, particularly with splenomegaly, in a previously healthy adult is highly suggestive of an acute hemolytic process. In congenital hemolytic anemia there is often the history of the disease having been present since childhood, and the presence of a similar illness in other members of the family may be elicited. In this connection, blood studies on other apparently well

members of the family, such as were performed in this case study, are very valuable as a diagnostic aid. That the patient with the congenital form usually does not appear particularly ill has long been known and has recently been emphasized by Kracke<sup>7</sup> who states, "the patient with the congenital type is more icteric than sick and the patient with the acquired type is more sick than icteric."

Spherocytosis and an increased fragility test are almost invariably present in the congenital type, but either or both may be absent in the *acquired* type. Bone changes may also occur in the congenital type, but have not been reported in the acquired form. The presence of biliary calculi has been cited as indicative of the congenital form though Mason has noted this complication in the chronic form of acquired hemolytic anemia. All other causes of hemolytic anemia must be excluded. In a patient who has atypical pneumonia, or who is taking sulfonamides, or who has leukemia or Hodgkin's disease, the etiologic factor may be readily evident. However, in the absence of these more common conditions, the less frequent causes of acute hemolysis such as exposure to industrial poisons, ingestion of fava beans or the presence of a tropical fever must also be considered. When these disorders are excluded as possibilities, the diagnosis of acquired hemolytic anemia of unknown etiology is acceptable.

*Leukemia* may be simulated because of the extreme myeloid hyperplasia with the presence of myelocytes and even myeloblasts in the blood. Large numbers of myeloblasts, characteristic of acute leukemia are, however, not found in acquired hemolytic anemia. The acute blood destruction present in this disease, however, does not occur in leukemia. In the patients with the fulminating type with hemoglobinuria, other causes of hemoglobinuria must be considered. It should be kept in mind that hemoglobinuria is merely a symptom which indicates severe intravascular hemolysis. Kracke and Hoffman<sup>15</sup> have recently emphasized the diagnostic significance of hemoglobinuria.

### PROGNOSIS

The disease may be self-limited and either death or recovery occur in from two to six weeks. Recovery may be spontaneous in some cases, whereas in others dramatic improvement may follow even a single transfusion, so that some authors consider that normal blood may possess an antihemolytic property. To this particular group of cases the term "Lederer's anemia" has often been applied. Most observers however, now agree that there is no justification for such a designation, inasmuch as this type of the disease represents merely one form of acquired hemolytic anemia.<sup>6, 10</sup> In other types not responding to blood transfusions striking results have followed splenectomy. In addition there is a group in which neither transfusion nor splenectomy is of any value in terminating hemolysis. It is of interest that in Damashek's

series of eighteen patients with acquired hemolytic anemia in whom splenectomy was performed, ten made a full recovery and eight died after splenectomy, four of these with continuing hemolysis<sup>10</sup> In Mason's series of twelve patients five died, in three of these cases splenectomy had been performed This is in contrast to the congenital type in which the patient usually makes an excellent recovery after splenectomy When evaluating the results in the acquired type, it should be kept in mind that in patients who demonstrate continuing hemolysis after several transfusions and in whom splenectomy is not performed the mortality is almost 100 per cent. At present there is no definite method of value in predicting the outlook in a given case Damashek feels that the presence of an unusual number of nucleated red cells, such as occurred in this patient, and of marked myeloid hyperplasia with or without bilirubinuria is a bad prognostic sign Davis points out that in eighteen cases with increased red cell fragility in which splenectomy was performed, improvement occurred in twelve cases, while in twelve cases with normal fragility only one improved.<sup>9</sup>

In some patients who recover after splenectomy, the response to operation may be immediate The jaundice subsides, the anemia rapidly improves, and agglutinins or hemolysins usually disappear The reticulocytes may remain high from two to three weeks after operation. The leukocyte and platelet counts may sometimes rise to unusually high levels

In none of the recovered patients in Damashek's series did hemolysis recur Mason,<sup>9</sup> however has emphasized that though splenectomy in the acute stage may be life saving, some of these patients may subsequently manifest a chronic course interrupted by hemolytic crises of variable intensity In his series of twelve patients, five were of this type. He points out that in the chronic stage the disease may be complicated by obstructive jaundice fibrosis of the liver, and biliary calculi.

#### TREATMENT

When this disease is recognized, treatment should be prompt. *Blood transfusions* should be used not only to replace the diminished red cells and hemoglobin but also because they may have a dramatically curative effect There are, however, some precautions which should be observed in administering blood transfusions in these patients First, because of the presence of possible hemolysins and agglutinins in the patient's serum, donors of the same group as the patient should be employed wherever possible It should be remembered that the serum of the universal donor, Group O (Type 4 Moss) contains agglutinins a and b Intragroup agglutination should be watched for, particularly in Group A patients and those who are Rh negative and who have had several transfusions. Damashek and Levine<sup>17</sup> have recently reported the



development of anti-Rh agglutinins in an Rh-negative patient with acute hemolytic anemia, who received a number of transfusions. The blood typing should be done by the Landsteiner-Levine technic and tests for auto- and isohemolysins should be performed. Icebox ( $4^{\circ}\text{C}$ ), room ( $20^{\circ}\text{C}$ ) and incubator ( $37^{\circ}\text{C}$ ), temperatures for the cross-matching should be used. The use of washed resuspended Group O red cells may offer considerable advantage in those patients in whom repeated transfusions are needed, in those who manifest hyperproteinemia, in those who develop reactions following whole blood transfusions and in those who demonstrate intragroup agglutinins, such as Rh-negative individuals.

The administration of *alkali* is of value in preventing the formation of acid hematin in the kidney tubules. If the patient tolerates it, large doses of sodium bicarbonate, 10 to 20 gm in twenty-four hours, may be given by mouth, otherwise 200 to 400 cc of a 2 to 3 per cent solution can be given intravenously. Iron therapy is not necessary, since the iron from the destroyed red cells is available for utilization. *Liver extract* may be used in patients who show evidence of bone marrow exhaustion or continuing hemolysis, though most of the patients with this disorder show intense bone marrow activity.

If improvement follows one to three transfusions given at intervals of twenty-four to seventy-two hours, no other therapy is indicated. When the patient continues to have hemolysis, however, after several transfusions, it is the consensus that *splenectomy* should be performed and that one should not wait too long before resorting to this procedure.<sup>16</sup> There is a tendency among some clinicians to feel that the patient will not be able to withstand the operation, but it should be recognized that without splenectomy the outcome is often hopeless. There is no doubt that in a number of cases splenectomy has been life-saving. Spinal anesthesia is probably preferable. The operation should be done as rapidly as possible by a skilled surgeon, and the possibility of an accessory spleen considered at the time of the laparotomy. Blood transfusion may often best be delayed particularly in a patient who has had reaction to previous transfusions until the spleen has been removed, or until the splenic artery has been ligated. Some observers prefer the injection of 1 cc of adrenalin into the spleen preparatory to removal, though others feel that this may discharge the hemolysin that may be in the spleen into the circulation. The administration of heparin and dicoumarin have been suggested following splenectomy to avert the thromboses that are often found at autopsy, presumably due to postsplenectomy thrombocytosis. The advisability of this procedure would seem to be as yet open to question, unless there is clinical suspicion of thrombosis. In the patient in whom severe hemolysis continues after splenectomy, therapy is usually hopeless and one has no recourse other than to resort to transfusions as was done in the case herein reported.

## BIBLIOGRAPHY

- 1 Wintrobe, M. Clinical Hematology Philadelphia, Lea & Febiger 1943 p 370
- 2 Singer K. and Damashek W. Symptomatic Hemolytic Anemia. Ann. Int. Med., 15 544, 1941
- 3 Bethell, F., Sturgis C., Mallery O and Rundies, R. Progress in Internal Medicine, Blood A Review of the Recent Literature. Arch Int. Med., 74 36, 1944
- 4 Damashek, W., Greenwalt, T and Tat, R. Erythroblastosis Foetalis (Acute Hemolytic Anemia of the Newborn) Preliminary Report. Am. J. Dis. Child., 65 571, 1943
- 5 Stats, D and Wassermann L. Cold Hemagglutination—Interpretative Review Medicine, 22 363, 1943
- 6 Mason, V. Acquired Hemolytic Anemia Arch Int. Med., 72 471 1943
- 7 Kracke, R.. Diseases of the Blood Philadelphia, J B Lippincott Co., 1941, p 244
- 8 Damashek, W. Medical Progress Hematology New England J Med., 230 542 1944
- 9 Davis, L. Haemolytic Anaemias. Edinburgh Med J., 50 589 1943
- 10 Damashek, W and Schwartz, S. Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type) Medicine, 19 231 1940
- 11 Reisner, E. and Halkstein, M. Autohemolytic Anemia with Auto-agglutination Improvement after Splenectomy Am J Med. Sc., 203 313 1942
- 12 Atkinson, F. Lederer's Anemia Brit. J. Dis. Child., 37 35 1940.
- 13 Miller E., Singer K. and Damashek, W. Use of Daily Fecal Output of Urobilinogen and Hemolytic Index in Measurement of Hemolysis. Arch Int. Med., 70 722 1942
- 14 Farrar, G., Burnett, W and Steigman, A. Hemolytic Anemia and Hepatic Degeneration Cured by Splenectomy Am. J. Med. Sc., 200 164 1940
- 15 Hoffman B and Kracke, R.. Hemoglobinuria Clinics, 2 179, 1943
- 16 Damashek, W. Management of Acute Hemolytic Anemia and Hemolytic Crises. Clinics, 2 118, 1943
- 17 Damashek, W and Levine, P. Isoimmunization with Rh Factor in Acquired Hemolytic Anemia New England J Med., 228 641, 1943

# THE FUNDAMENTAL IMPORTANCE OF DIET IN THE TREATMENT OF PEPTIC ULCER IN AN ARMY GENERAL HOSPITAL

With Special Reference to Vitamin "U" Therapy

MAJOR VIRGIL J. GIANELLI AND CAPTAIN VINCENT BELLAFFIORE  
MEDICAL CORPS, ARMY OF THE UNITED STATES

FROM October 1942 to January 1943, patients with peptic ulcer on the Medical Service at Hammond General Hospital received two types of management. These different regimens were not planned previously but occurred as a result of the patients being observed on two separate sections of the hospital. The enlisted patients, who were cared for on the Gastrointestinal Section, received no routine medication, the treatment consisting mainly of the use of the army convalescent ulcer diet<sup>1</sup>. The officer patients, who were cared for on the Officer Section, on the other hand, received a Sippy type of dietary regimen with routine medication consisting of alkalis, antispasmodics and sedatives. The clinical impression was obtained that the patients in the two groups appeared to fare equally well.

As a result of these observations, a type of regimen for ulcer patients emphasizing the dietary management was instituted. This regimen has been employed at this hospital since January 1943 and the observations made comprise the basis of this report. A small group of patients who did not respond to treatment with the ordinary convalescent ulcer diet were treated by the use of a diet rich in vitamin "U". The use of vitamin "U" diet and the response obtained in some patients in this group of recalcitrant ulcer cases observed at this hospital has been reported<sup>2</sup>. The importance of diet in the management of patients with ulcer in the military service has also been noted by others<sup>3</sup>.

## SOURCE OF CASES STUDIED

From January 1, 1943 to August 1, 1944, 11,411 enlisted personnel were admitted as patients to Hammond General Hospital. Of this number, 793 or 6.9 per cent were admitted to the Gastrointestinal Section of the Medical Service. This group of cases did not include patients whose condition was diagnosed as "neurasthenia gastrica" at the time of admission, as these patients were cared for on the Neuropsychiatric Service. Four hundred and seventy-eight or 60.3 per cent of the patients admitted to the Gastrointestinal Section were diagnosed as having peptic ulcer. In 442 or 92.5 per cent of these patients the ulcer was duodenal and in thirty-six or 7.5 per cent the lesion was gastric.

These patients were received from three main sources. The first and largest group was returned from overseas and these patients invariably had undergone weeks to months of treatment before departure from overseas but a few had developed recurrence during transportation by ship. The second group of patients was received from nearby station hospitals because they were not completely relieved by the type of management which had been carried out and because they were considered to require prolonged hospitalization. Nearly all of these patients presented definite symptoms of ulcer and many showed ulcer craters by x-ray. A third group of five patients was received from the Post Detachment and all of these presented active peptic lesions.

#### METHOD OF INVESTIGATION

A special effort was made to secure an accurate history of each patient's symptoms and treatment both in civilian life and in military service. Emphasis was placed on obtaining a detailed account of the diet at the time the patient developed symptoms in Army service. All previous military hospital data referable to the patient's illness was recorded chronologically on the clinical record.

On physical examination particular attention was paid to the patient's body habitus, state of nutrition, and the presence of localized epigastric tenderness. Early in the course of this study it was noted that the patients did not conform to any particular body type and that the distribution of body configurations was about the same as in any average group of young male adults. This observation was true during the entire eighteen months of the study. If the majority of patients with peptic ulcer in civilian life are tall, slender, nervous and apprehensive and tend to be psychoneurotic, it is possible that they seek medical aid and that a diagnosis of ulcer is made, so that they do not meet the requirements for entry into the military service. Inasmuch as approximately 90 per cent of the patients with peptic ulcer admitted to this hospital had symptoms indicative of the presence of that disease prior to induction, it is evident that their complaints were not dominant factors in their lives, that they were more stoic about them and that they did not visit doctors frequently. Many of this group had never consulted a physician concerning their recurrent indigestion and almost none of them had ever undergone a complete gastrointestinal investigation in civilian life. They were rarely given the proper diagnosis and readily passed Army induction examinations.

The usual routine laboratory procedures were carried out in all cases, including urine examination, blood count, blood Kahn test, stool analysis for blood, ova and parasites and gastric analysis by the alcohol test meal method. Gastrointestinal x-ray study was made even though recent gastrointestinal x-ray reports from other hospitals were available. In patients with gastric ulcer and in the majority of patients with gastric symptoms in whom the diagnosis was in doubt, gastroscopy

was also performed. All the patients suspected of having peptic ulcer received a thorough diagnostic investigation before a decision was made on the exact mode of therapy.

All patients on the section were seen by a consultant neuropsychiatrist if their symptomatology suggested that such a consultation was indicated. These patients were given clearance by the consultant in nearly all instances. It is of interest in this connection to note that during a three-months' period sixty-nine patients with persistent abdominal complaints were transferred from the Neuropsychiatric Service to the Gastrointestinal Section and in only one instance was a peptic ulcer found.

#### ROUTINE MANAGEMENT

**Rest and Exercise**—Except for a few patients with severe pain or with evidence of complications, all were allowed to be ambulatory and to leave the wards from time to time. One patient developed a perforation while remaining in bed, two patients were maintained at bed rest because of active bleeding, and one patient was restricted to bed rest because of partial pyloric obstruction. Ambulatory patients regularly indulged in the mild physical exercise regimen of Class IV as conducted by the Reconditioning Division and patients who in later convalescence were symptom-free carried out the more vigorous Class III calisthenics and sports, including volley ball. At one time eight symptom-free patients were transferred to the advanced Reconditioning Center and took part in a program requiring vigorous physical exercise including drills, hikes and various active sports. Provision was made for these patients to receive the convalescent ulcer diet and to obtain milk regularly between meals. All of these patients developed recurrence of symptoms and five showed fresh ulcer craters by x-ray.

**Diet**—Except for a few who manifested severe pain, or who presented signs of complications as noted, all patients started therapy on a convalescent ulcer diet. This diet was given according to War Department Technical Manual 8-500, a manual of hospital diets published August 13, 1941.<sup>1</sup> This diet consists of beverages made with milk, toast, white or graham bread, butter, moderate amount, cereals, refined, cooked or uncooked, cheese, cottage, cream and bland, desserts, bland, such as custards and puddings, eggs, any style, except fried, meat, scraped beef and bacon, fruit, cooked and strained, soup, creamed and puréed only, vegetables, strained and puréed only. No nuts, salads, sweets or condiments are permitted. Certain additions and modifications to this standard hospital diet were utilized and are considered valuable adjuncts. First, meat such as tender lamb or beef, usually ground, and fish or fowl were served once or twice daily from the beginning. Second, orange and tomato juices were served to all patients who accepted them readily. A few patients did not like these juices but very rarely did any patient maintain that these gave him

indigestion Raw bananas were served when available Soft vegetables such as summer squash, stewed tomatoes, carrots, beets, spinach, green peas, tender string beans, and asparagus tips were served without straining or puréeing Seedless jams and nutless candy were permitted The special convalescent ulcer diet rich in vitamin 'U' includes certain other food additions and is described below

**Medications**—No medications were given routinely Patients were permitted to take a Sippy powder or bicarbonate of soda symptomatically early in the course of their illness for symptomatic relief Antispasmodics were not used and sedatives were never given regularly Occasionally mild sedation was utilized for pronounced insomnia No attempt was made at alkalization as part of the treatment, and consistent sedation was not utilized in any case The majority of patients in this series received no medication for ulcer at any time during their hospital stay Certain medications were utilized in conjunction with the special vitamin 'U' convalescent ulcer diet These are discussed below

**Gastric Lavage**—This procedure was carried out only as a therapeutic measure in one patient who had pyloric obstruction, and who thus obtained symptomatic relief

**Alcohol**—Though the use of alcoholic beverages was forbidden, many patients left the hospital on authorized pass from time to time and a number of these obviously drank spirituous liquors In some of them an exacerbation of symptoms which could be attributed to the use of alcohol developed, but these symptoms usually subsided without special therapy

**Tobacco**—Patients were not limited in the use of tobacco and many smoked twenty or more cigarettes daily No untoward symptoms could be attributed to the use of tobacco in the form of cigarettes and in no case did the ultimate course of the illness seem to be affected in an untoward manner

**Psychotherapy**—Individual psychotherapy by a trained psychiatrist was not utilized in any of these patients The few who might possibly have benefited from this form of therapy were ultimately separated from the military service, by disability discharge

#### SPECIAL CONVALESCENT ULCER DIET WITH VITAMIN U

The use of a more liberal high caloric diet in the treatment of patients with peptic ulcer is not new The Meulengracht diet of 'treatment by food' is an established and widely used therapeutic procedure The special diet used at Hammond General Hospital is not only high in calories but also contains certain uncooked foods in addition to milk, such as raw eggs, large amounts of butter, fresh greens and olive oil, considered to be rich in anti-ulcer factor This anti-ulcer factor designated as vitamin "U" has been shown to be effective experimentally but has not thus far been proved to have a

therapeutic effect in the management of patients<sup>4</sup> However, the results of therapy in thirty-one cases on this dietary regimen which includes vitamin "U" have recently been reported by Cheney<sup>2</sup> All the patients reported by him had failed to respond to conventional forms of therapy Improvement was found to be highly satisfactory in twenty-seven or 81 per cent of these cases

Of the 478 patients treated in the present group at this hospital, forty failed to show satisfactory response to the regular convalescent ulcer diet. The failures were placed on the special dietary regimen Each of these forty patients complained of persistent abdominal pain With one exception, all showed positive x-ray evidence of active ulceration despite long periods of previous therapy Many who were undernourished had failed to gain weight satisfactorily These patients received the following food additions to the regular convalescent ulcer diet

Breakfast Eggs 2, cooked 2½ minutes Butter, 2 pats (20 gm)

10 A M Eggnog, ⅓ liter

Dinner Butter, 1 pat (10 gm)

Salad, 1 serving with special olive oil dressing

3 P M Peanut butter sandwich (with or without jelly)

30 gm peanut butter (smooth)

1 pat butter (10 gm) Eggnog, ⅓ liter

Supper Butter, 1 pat (10 gm)

8 P M Eggnog, ⅓ liter

The eggnog formula 4 eggs (200 cc), sugar, 30 gm, vanilla, 2 cc, 20 per cent cream, 200 cc, milk, 550 cc

Salad may contain any or all the following lettuce, broccoli, watercress, romaine, parsley, tomato, avocado (all fresh)

Salad dressing recipe lemon juice, 160 cc, olive oil, 320 cc, salt, 10 gm, sugar, 30 gm.

This diet consists of approximately 4200 calories and contains approximately 150 gm of protein, 450 gm of carbohydrates and 250 gm of fat

Certain medications known to contain vitamin "U" were included in the treatment First, cerophyl tablets which are made from green grass stalks were given in a dose of 5 tablets (2.5 gm) three times a day after meals and five tablets at bedtime Second, hog stomach extract in the form of ventriculin was given in a dose of 15 gm three times a day Also, bile salts (Bilron) were regularly administered in half gram doses three times a day after meals, as they had been shown to be effective in enhancing the activity of vitamin "U" presumably by promoting the absorption of this fat soluble substance No other form of routine therapy was utilized

These patients remained on this dietary and medicinal regimen for

an average period of one month. Those in whom rapid relief was obtained were treated for a shorter period, whereas those in whom symptoms tended to persist or in whom weight gain was not satisfactory were treated for a longer period of time. Three patients had to be eliminated from this series because of lack of cooperation or for administrative reasons. All of thirty-seven who were able to follow the treatment in detail showed some improvement and thirty-four patients obtained complete relief. X-ray studies made after treatment showed negative findings or revealed only a persistent deformity of the duodenal cap indicative of quiescent ulcer. Approximately 80 per cent of the patients who were underweight gained 5 pounds or more during treatment. The three patients who did not improve as satisfactorily as the others continued to complain of some distress despite a lack of x-ray changes indicative of active ulceration. Two patients who were considerably underweight failed to gain weight although they became symptom-free rapidly and x-ray evidence of ulceration disappeared.

#### ILLUSTRATIVE CASES

The following three case reports illustrate the benefit of dietary therapy in the management of patients with peptic ulcer.

##### *CASE I—Duodenal Ulcer of Recent Origin Healed on Dietary Therapy Alone*

—The patient was a 32 year old sergeant with one year and eight months of service, the last thirteen months of which were spent overseas. He stated that he first developed indigestion in March 1944 while on field rations. This consisted of upper abdominal, postprandial pain relieved by milk and alkalis. The pain usually recurred about one hour after eating and was particularly bothersome at night, often awakening him three to four times. He was returned to the main land and entered this hospital on June 21, 1944, three months after the onset of symptoms. He had followed a prescribed diet and taken medication continuously during this time, but his condition had not improved materially.

Moderate epigastric tenderness was present on physical examination. A gastrointestinal x-ray series showed a constant deformity of the duodenal cap with an ulcer crater. Gastric analysis revealed highest total acidity of 62 degrees and highest free hydrochloric acid of 50 degrees.

On June 22, 1944, this patient was placed on a convalescent ulcer diet. On June 26 he was still having considerable discomfort so that he was placed on more frequent feedings, receiving milk and cream, one glass every four hours from 7 A.M. to 10 P.M. If he awoke during the night he was given more milk and cream. Divided portions of bland foods such as rice, potatoes and toast, and additional orange juice, were also added to the diet. By July 10 the patient was symptom free and was returned to the original convalescent ulcer diet. He continued symptom free. The gastrointestinal series was repeated on August 15 and showed a residual deformity of the duodenal cap but there was no tenderness, irritability or spasm and no ulcer crater was demonstrable.

*Comment*—This patient experienced persistent ulcer pain for three months despite dietary and medicinal therapy, but finally obtained complete relief from an adequate dietary regimen without any medications.



*CASE II—Symptoms of Duodenal Ulcer Responding Only to the Special Dietary Regimen*—The patient was a 31 year old technician, fifth grade, colored, with two years and four months of service, thirteen months of which were spent overseas. Upon entry to this hospital April 4, 1944, he stated that he had intermittent, recurrent epigastric pain since July 1943, which was relieved in the past on a Sippy regimen. He states that prior to July 1943 he had no similar complaints. A review of the transfer chart revealed that he had been treated with some type of ulcer regimen since July 15, 1943, at which time an x-ray series revealed a duodenal ulcer crater and a diagnosis of duodenal ulcer was made. He had received several trials of medications before entry to this hospital, including milk with calcium carbonate, gelatin solution, Sippy powder No. 2, tincture of belladonna and sodium amytal.

When this patient entered this hospital, he was having epigastric pain before meals, relieved by food, and was also complaining of considerable night pain. He weighed 133 pounds, which was 22 pounds below his normal weight. Gastric analysis revealed hyperchlorhydria with a total acidity of 75 degrees and a free hydrochloric acid of 57 degrees. An x-ray series showed a deformed duodenal cap with an ulcer crater. He was placed on a regular convalescent ulcer diet, but improved very slowly. On May 3 he was transferred to the Advanced Reconditioning Center. The convalescent ulcer diet was continued but the symptoms persisted and he failed to gain weight. On May 22 he was returned to the hospital for a repeat of the gastrointestinal x-ray series which revealed that the duodenal ulcer crater was still present. On May 23 he was placed on the special convalescent ulcer dietary regimen and by May 30 he was symptom-free for the first time. By June 28 his weight was 154 pounds, so that in thirty-six days on the special convalescent ulcer diet he had gained 21 pounds. On June 26 a gastrointestinal x-ray series showed no evidence of ulcer crater and no irritability of the duodenal cap.

*Comment*—This patient failed to respond to the conventional forms of dietary and medicinal therapy, but improved rapidly on the special dietary regimen containing Vitamin "U."

*CASE III—Chronic Peptic Ulcer Relieved by Diet*—This 34 year old staff sergeant with one year and nine months of service, none of which had been overseas, entered this hospital May 1, 1944. He gave a history of having first developed "indigestion" five years previously, and although x-ray investigation had never been undertaken he had been placed on a modified Sippy diet. He stated that in civilian life it had been his practice to follow this diet for periods of several weeks to several months after which he would abandon the treatment. After a few months the symptoms would recur, so that he would then again return to the Sippy diet to obtain relief. At the time of induction into the Army he was symptom-free and remained so until January 1944 when he was admitted to the hospital for two weeks because of duodenal ulcer. He returned to duty but on April 7 because of recurrence of symptoms he was again admitted to the Station Hospital and was then transferred to Hammond General Hospital.

Gastric analysis revealed hyperchlorhydria with total acidity of 90 degrees and free hydrochloric acid of 68 degrees. An x-ray series showed a deformed, irritable, tender, duodenal cap but no evidence of ulcer crater. He was placed on a convalescent ulcer diet and on June 12, after clinical improvement, he was transferred to the Advanced Reconditioning Center. At this time he was asymptomatic but the diet was continued. On June 30 he was readmitted to the hospital because of a return of his indigestion and on July 7 x-ray revealed a duodenal ulcer crater, with marked deformity, tenderness and irritability of the

duodenal cap On July 11 the special convalescent ulcer diet and medications were started His weight at this time was 145 pounds which was 10 pounds under his normal weight In three days he was symptom free but he had brief recurrences of pain on two occasions during the month of July Once, this recurrence of pain followed his participation in organized exercises. On August 8 a gastrointestinal x ray series was repeated and although a deformed cap was found, there was no tenderness, irritability or evidence of ulcer crater His weight was 149 pounds.

*Comment*—This patient is illustrative of the type of individual who has had a history of peptic ulcer for a number of years before entering the Army and who in civilian life was able to find an environment compatible with his disability He had recurrences of ulcer symptoms in the Army He responded to the regular convalescent ulcer diet until he was exercised regularly when an ulcer crater developed. He then showed rapid improvement on the special dietary regimen, with x-ray evidence that the ulcer had healed.

#### SUMMARY AND CONCLUSIONS

1 A total of 438 patients with peptic ulcer were clinically cured while taking a liberal convalescent ulcer diet. These patients received no routine medications of any kind Almost all of them were ambulatory throughout the course of therapy and all were permitted the use of tobacco

2 Thirty-seven additional patients who were not relieved while taking the convalescent ulcer diet were placed on a special high caloric convalescent ulcer diet containing raw foods and medications known to be rich in an anti-ulcer factor, vitamin "U", which has been shown to be effective in the treatment of experimental peptic ulcer Thirty-four of these patients (92 per cent) were completely relieved on this regimen

3 Although the use of dietary treatment alone has proved highly satisfactory in the management of patients with peptic ulcer in this series, it is recognized that this method of therapy may not be applicable to all patients with peptic ulcer and that other forms of treatment may be indicated in selected cases.

#### BIBLIOGRAPHY

- 1 War Department Hospital Diets. Technical Manual 8-500 par 21-22 and 117-128 1941
- 2 Cheney G Peptic Ulcer and Nutrition. The Military Surgeon 95:446-457 1944
- 3 Palmer W L. Stomach and Military Service. J.A.M.A., 119 1155-1159 1942
- 4 Cheney G Cinchophen Gastric Ulcers in Chicks Archives of Internal Medicine, 70:532-557 1942

# SYMPOSIUM ON REHABILITATION

---

## INTRODUCTION

In a democracy every soldier has the right to expect the best equipment, the best food and clothing, and the best medical care. These things the American soldier has received and his record in combat attests how well he has used them. The scope of medical care in World War II has increased tremendously. It has been broadened to encompass not only definitive medical and surgical care, but new fields in preventive medicine and sanitation have also been explored and conquered. New concepts in the management of convalescence and rehabilitation have been created. The battle against disease and injury is not won when the last drop of sera has been given or the last suture placed in the incision. It is not won until the wounded veteran has been motivated, retrained, and reoriented for a useful, productive place in the community, either military or civilian. It is to fulfill this obligation that the armed forces have established comprehensive programs of rehabilitation and that certain vocational and educational opportunities have been made available to the veteran by congressional action.

But what has the disabled citizen in a democracy the right to expect? In the great manpower shortage which accompanies total war, the disabled citizen has proved his ability to produce as well as the normal man if he is placed in the proper niche. Industry has employed thousands of handicapped workers and has found that they have no handicap, if they are properly placed. Their production record, accident rate, and absentee record have equalled, or even excelled, the records of their normal co-workers. These people have *earned* the right to work, they have proved that they can do the job. It is up to the democracy to see that they are given the opportunity.

Rehabilitation is primarily a medical problem, but the doctor alone cannot *begin* to accomplish this mission. It is a job for team work, the doctor as captain of the team of specialists in the whole broad field of rehabilitation—physical educators, physical therapists, psychologists, occupational therapists, social workers, vocational guidance experts—all working together to treat the **WHOLE** man. We as physicians must rededicate ourselves to the treatment of the patient, not alone the disease. We must know the science of medicine but practice the art. We have new responsibilities and new opportunities in this great field of rehabilitation. It is our job to do.

HOWARD A. RUSK  
Colonel, Medical Corps  
Chief, Convalescent Services Division,  
Office of The Air Surgeon

# CONVALESCENT CARE AND REHABILITATION IN THE ARMY AIR FORCES

## A New Challenge of Postwar Medicine

COLONEL HOWARD A. RUSK\*

MEDICAL CORPS, ARMY OF THE UNITED STATES

THAT all wars make some constructive contribution has once again been demonstrated by the technological and scientific advances, necessary for survival, made in this present conflict. Medicine has kept pace with these advances by new research and study on the care of the human body when exposed to the stresses and strains of new and abnormal physiological requirements—in the stratosphere, under the sea and on the surface of the earth. We have learned much of how man must adjust his physiological mechanism to meet the rigors of these strange, new and often terrifying environments. It is not, however, man's body alone that is affected by the rigors of war, it is probably psychologically and emotionally that he pays the greatest toll.

Medicine has accepted the challenge of total war and the great advances which have been made are not only in the scientific and technical fields but also in those of human relationship. The bond between the patient and the doctor has had a rebirth. Thousands of doctors and millions of men are coming out of this war with closer ties than ever before. The science and art of medicine have become welded inextricably to meet the physical and spiritual needs of man.

This has been particularly true in the field of convalescent care and rehabilitation, where a close patient-doctor relationship has become the keystone of the treatment and management of casualties returned from combat theaters. Early in the war when the conservation of manpower made necessary a comprehensive program, in order to reclaim every man possible for the military service, the Army Air Forces formulated a program based on this concept.

In those uncertain days, every man hour of training in the Air Forces was unbelievably important. Our radio schools, mechanics schools and flying schools worked around the clock, twenty-four hours a day, seven days a week. In spite of this emphasis we still had in our military hospitals thousands of men who had completed their definite medical care and now merely sat around waiting for time to complete their convalescence. These hours spent in boredom without any purposeful activity did not contribute to the mission of the Army Air Forces.

---

\*Chief, Convalescent Training Division, Office of the Air Surgeon, Washington, D. C.

## THE AAF CONVALESCENT TRAINING PROGRAM

It was in an effort to provide for the purposeful utilization of this hitherto wasted time and to provide a program of activity which would be an adjunct to the definite medical care of the sick soldier that General H H Arnold, Commanding General of the Army Air Forces, in December 1942, ordered that a Convalescent Training Program be established in all AAF hospitals under the direction of Major General David N W Grant, MC, the Air Surgeon, since its inception at that time, over sixty million man-hours of physical and educational training have been given in Army Air Forces hospitals—sixty million man-hours of productive time which would have been wasted. The teaching rate at the present time is in excess of four million man-hours per month.

A Convalescent Training Program is provided for the ordinary sick precombat trainee as well as for the battle casualty. Physical reconditioning is accomplished by a systematic, graduated series of calisthenics and corrective exercise. These are first given in their mildest form even to bed patients. The exertion is gradually increased as the patient's physical tolerance and general condition improves until he is able to participate in a fully organized program of drill, hikes, active recreation and fatigue duties. Exercises begin in bed postoperatively as soon as the patient's condition permits, which prevents muscular atrophy of the unaffected parts and general deconditioning. A pneumonia patient begins deep breathing, hand, arm and chest exercises as soon as his temperature is normal. This simple, early exercise routine not only improves the muscle tone of the patient but is an excellent morale factor.

Designed for a dual mission, the Convalescent Training Program aims, first, to send the soldier back to duty in the best possible physical condition in the shortest period of time, secondly, to teach the soldier-patient something that will make him a more efficient and effective fighting man. Under this plan, physical activity and military education have become as much a doctor's prescription as drugs and diet. Muscles are not permitted to atrophy, for reconditioning exercises start the moment the acute illness or surgery is terminated. Minds do not become stagnant. Time formerly wasted in reading comic books and adventure stories is spent purposefully. The classroom has been moved into the wards, and training films, chemical warfare classes, radio code practice periods and discussions on why we fight and the postwar world have become an integral part of the hospital day. Radios, carburetors and even airplane engines are brought into the wards and the sun rooms. The hospital has been transformed into a combination gymnasium, schoolroom, machine shop and New England Town Hall.

## PHYSICAL REHABILITATION

Early in the program it was noted that, to obtain maximum results, reconditioning had to start at the earliest possible moment following acute disease or injury, and it had to be *purposeful* and *progressive*, starting with bed exercises taken ten minutes twice daily and gradually increased to four or five hours a day of physical activity. Special corrective exercises were designed to meet the military needs and experienced physical training instructors assigned to administer them. A positive attempt was made to correlate ward fatigue and detail work with the soldier's disability to aid in functional recovery. Men with hand, finger and wrist injuries were given fatigue duties that involved finger and hand manipulation while those with bad backs or knees were given duties which aided in their recovery by strengthening the affected part. A special booklet, AF Manual No 23, *Handbook of Recovery*,<sup>1</sup> was designed as a prescription blank for all types of orthopedic injuries, a nine-page section on anatomy, physiology and pathology, written in simple language, demonstrating to the GI soldier why he is in the program, the value and effect of active exercise, how bones, muscles and nerves are made, what happens when they are injured, and how they heal, a two-page descriptive prescription for the specific injury, which shows the soldier-patient by diagram the normal function of the affected part, his diagnosis, the type of physiotherapy prescribed, illustrated active exercises to be done with and without supervision, and a personal objective recovery chart which the patient maintains himself. This has been a very effective innovation, as it not only gives the patient an insight into and understanding of his condition but by competing with himself, a greater motivation. An accompanying instructors manual,<sup>2</sup> AF Manual No 24, *Handbook for Physical Retraining*, has been prepared for the guidance and use of the physical reconditioning instructors in order that they may properly administer and supervise the exercises so as to obtain maximum results.

Another publication which is meeting with widespread approval is the crutch-walking handbook, AF Manual No 49, *Let's Walk*.<sup>3</sup> Unique in its presentation, this booklet deals with the functional aspects of walking with the use of aids. It first gives the patient a brief, psychological orientation to his disability and then proceeds to demonstrate objectively through the use of illustrations and charts the factors involved in walking with aids, the muscles which must be utilized and therefore strengthened to use walking aids effectively, the techniques and gaits of walking, practical hints on the care of the aids, and, most important, insight and motivation.

**End Results**—More interesting, however, and perhaps more than the means used to meet our objectives, are the ends. The experience with the Convalescent Training Program twenty-eight months has contributed some interesting the pertinent observations are that

- 1 Hospitalization time has been shortened,
- 2 Hospital readmissions have been reduced,
- 3 Sick leave has been practically eliminated except in extraordinary cases,
- 4 The morale of the soldier-patients has been immeasurably improved, for they have been kept interested and busy in purposeful activity

A number of interesting clinical studies have been made. Van Ravenswaay and his co-workers<sup>4</sup> studied 645 patients with virus pneumonia, treated in one acute ward. They were then assigned to alternate convalescent wards. In Ward I, "nature was permitted to take its course" men sat around and went back to duty when they and the medical officer felt they were able. In Ward II they were kept in bed until their sedimentation rate had reached 10 mm in one-half hour and they were then put in a reconditioning program, beginning exercises for one-half hour the first day and increasing progressively until the twelfth day, when the patient was participating in a full six-hour day of physical training, mass games, competitive sports and active recreation, including a 10-mile hike. Group I averaged forty-five days of hospitalization, with a 30 per cent recurrence rate, Group II, at the end of thirty-one days, was discharged to duty, with but a 3 per cent recurrence rate. Forty-five days' hospitalization, unsupervised, thirty-one days with graduated conditioning—a 30 per cent recurrence rate compared with a 3 per cent recurrence rate.

Karpovich and his associates at the School of Aviation Medicine, San Antonio, Texas, have studied a similar group of 200 aviation cadets convalescing from virus pneumonia<sup>5</sup>. Using a modification of the Harvard step test and starting as early as the first afebrile day, Karpovich found that by the reactions to this test it was possible to determine, with a degree of accuracy, the patient's ability to enter into, and the degree of participation in, the Convalescent Training Program activities. An interesting by-product of Karpovich's observations was that patients being tested required an average of five days less hospitalization time than those participating in the general program, which certainly points to the fact that these men can tolerate an even more strenuous reconditioning program.

Colonel Gilbert Marquardt, MC, Chief of the Medical Service at the AAF Regional Station Hospital No. 1, Coral Gables, Florida, has recently made an interesting observation on a small group of patients recovering from virus pneumonia<sup>6</sup>. These patients were clinically well but still had definitely positive x-ray findings. They were put on hyperventilation every waking hour, twelve times a day, and serial x-rays were made every twelve hours. Over 90 per cent of the patients in this series became x-ray clear in a period of ninety-six hours. Further studies are being made at this station, having the patients hyperventilated even during the febrile stages of the disease to

determine if such a procedure will aid in the prevention of patchy atelectasis

Early in the operation of the AAF Convalescent Training Program it was noted, clinically, that orthopedic patients requiring fixation of a specific member did not, if kept in top physical condition generally, show the usual degree of muscular atrophy in the fixed part and that when the cast was removed, they could be reconditioned to duty in approximately one-half the usual convalescent time. This has saved a tremendous number of noneffective man hours for the Air Forces. This clinical observation certainly gives food for further thought and physiological study.

**Physical Fitness Testing and Physical Training of Convalescent Rheumatic Fever Patients.**—As a part of the AAF Rheumatic Fever Control Program,<sup>7</sup> Karpovich, Weiss, Starr and Ershler have recently presented a preliminary report of their work on physical fitness testing and physical training of convalescent rheumatic fever patients.<sup>8</sup> Because of the chronic, recurrent nature of the disease and the possibility of disabling cardiac sequelae, it was felt that special emphasis must be placed on standardization of physical activity and convalescent training for these patients through building a group of graduated physical fitness tests which could be used in conjunction with clinical observation to determine the rate by which the patient could safely be permitted to progress to successively more strenuous physical activity. Using a modification of the Harvard step test with two benches 12 and 20 inches in height and a cadence of twenty-four steps per minute, physical testing was started when, in the judgment of the medical officer, the patient should be permitted to be out of bed in a chair. The first test involved twelve step ups in thirty seconds, using the 12-inch stool. Criteria for passing the test are a pulse rate less than 100 per minute one minute after the exercise and good coordination in the performance. If the patient passed this test and the medical officer concurred, he was allowed to be ambulatory in the ward. Using the same criteria the next test involved twelve step-ups in thirty seconds, using the 20-inch stool. In this test it was found that body metabolism in the average individual was raised eight to ten times. If this test was passed the patient was placed on a program of graduated ward calisthenics. These exercises were given for ten minutes twice daily to start, and over a period of approximately three weeks, they were then increased to thirty minutes twice daily. The exercises used at the start of this program have been found to raise body metabolism roughly three times. The degree of the exercises during this period was gradually increased to a level which raised the metabolic rate seven to nine times above normal.

The next level of physical fitness testing was designated the progressive test, consisting of twenty-four step-ups per minute to a 20 inch bench for a period up to five minutes. Scoring was based on the



duration of the exercise plus the pulse rate one minute after exercise. If the patient made a minimal passing score on this test and the medical officer in charge concurred, he was placed in the barracks phase of the program with a minimum stay of two weeks in each of four periods. In the first period, physical training was given for forty minutes daily, in the second phase, fifty minutes daily, in the third, seventy minutes daily, and in the final period, for ninety minutes. The intensity of the exercise was increased in each period and progressions were made only with concurrence of the medical officer in charge. Progressions from period one to period two were automatic after two weeks, but progression from period two to period three was dependent upon the score made on the progressive test. To date, approximately seventy patients have been used in the study with no recurrences or other untoward reactions.

Some five thousand patients of all types have been studied on their day of discharge from AAF hospitals with the standard AAF Physical Fitness Test, consisting of chin-ups, sit-ups and running against time. These patients averaged approximately 3 per cent better scores than the average made by troops on duty status at the same bases. It is felt that this is evidence of the fact that, following the hospital's Convalescent-Reconditioning Program, men are being returned to duty *ready for duty*.

**The Undesirable Effects of Bed Rest**—During the past year there has been tremendous interest in the physiological and psychological problems of bed rest, and already material is accumulating in the medical literature in this field, with many additional studies currently being carried on.<sup>9</sup> Keys,<sup>10</sup> working with conscientious objectors and studying them under carefully controlled conditions of complete bed rest for six weeks, in his preliminary observations has noted that these individuals' reaction time is reduced approximately 5 per cent, that coordination is markedly decreased, especially in the proprioceptive senses, that blood volume is reduced from 10 to 20 per cent, and there is a reduction on an average of 11 per cent in the size of the heart. He noted that in the standard work test, after a period of bed rest, there is a reduction of cardiac effectiveness with a relative tachycardia, both at rest and in work tests, work formerly done with a pulse rate of 125, on the first day after prolonged bed rest would often cause the pulse to reach 170. He noted further that it takes a period up to sixty days to recover normal pulse rate for the same work load. A mounting pulse rate even at complete bed rest under basal conditions was also observed, pointing to the increasing incapacity of the heart to maintain the circulation adequately. Keys also noted that it is very difficult to keep a patient in positive calcium balance, especially during the early days of bed rest, and that more than twice the amount of protein in the diet is necessary to keep the patient in normal nitrogen balance. There

is also a marked increase in the urinary output of thiamine and riboflavin

Clinical and laboratory investigations now under way point toward the necessity for a broad research program in this whole field and a better understanding by the medical profession of the deconditioning-reconditioning phenomena of the individual who is confined to bed

#### EDUCATIONAL RETRAINING

The second aspect of the AAF Convalescent Training Program for the precombat soldier-patient is a teaching program designed to increase his military knowledge and make him a better soldier. The educational program is designed to meet the needs of all special types of Army Air Forces installations. In basic training centers, the emphasis is on self-protection, gas warfare, camouflage, booby traps, map reading, care of equipment and medical aid. All types of training, orientation and morale films are used daily. Training aids, visual aids and handicraft, with model airplanes, tanks, ships and camouflage nets have proved of excellent educational and corrective therapeutic value.

Special classes have been organized both for the teaching of men educationally retarded and giving instruction in subjects such as mathematics and physics for patients scheduled to take later air crew or technical training. A daily summary of current affairs and an orientation course in military geography are a part of all curricula.

In the technical schools the program is modified to meet the special needs of the patient. At the radio schools, special code receiving sets and sending keys have been placed in the hospital wards so that men may continue to increase their skill even while in bed. During certain periods of the day the wards are blacked out and the men send and receive blinker code from bed to bed. Formerly it was noted that men would lose their code speed after a week without practice. Now our patients are leaving the hospital with maintained and, in many cases, *increased* speed.

In the hospitals serving the flying schools and tactical units, geography, geopolitics, airplane identification, reptile-insect-pest control lectures, lectures on arctic and tropical medicine and field sanitation are the subjects stressed. Medical officers have designed a series of patient-doctor talks to give the men a knowledge of the symptoms, cause, treatment and prevention of various tropical diseases. This has been of tremendous help in orienting these soldiers to their new environments and allaying the fear that comes naturally when going into unfamiliar surroundings.

#### ROLE OF THE AAF CONVALESCENT HOSPITAL

Based on observations of the medical, physical, psychological, vocational and social needs of men returning from overseas combat and a realization that the Convalescent Training Program as carried on in

AAF regional and station hospitals was not designed to meet these specialized needs, special AAF convalescent hospitals were activated on September 18, 1943. Originally known as convalescent centers and subsequently renamed "convalescent hospitals," they were at first attached to existing operating facilities but as the increased need and desirability of operating such facilities as independent units became apparent, the convalescent hospitals were relocated, often taking over entire army posts.

Operated by the AAF Personal Distribution Command, these hospitals provide convalescent training programs designed to meet the needs of the *whole* man, whatever they may be. Patients are admitted to these hospitals from ASF general hospitals, AAF regional and station hospitals upon completion of definitive medical care, directly from airports and seaports of debarkation, and from AAF redistribution stations, if in need of rehabilitation. Every skill and effort is centered on the task of reconditioning as many men as possible in the following sequence of possibilities:

- 1 Return to an AAF assignment in original military occupational specialty,

- 2 Return to an AAF assignment in a new military occupational specialty compatible with civilian and military education and experience and physical condition,

- 3 Return to civilian life as self-sufficient individuals, both socially and economically,

- 4 Discharge to the Veterans Administration.

**Program for the Soldier-Patient Who Is to Be Reactivated**—For the soldier-patient who is to return to duty status there is an intensive program of physical rehabilitation, educational retraining, psychological readjustment, and resocialization. Men are brought to the peak of physical fitness through competitive team play, progressive and graduated calisthenics, and active recreation, which includes athletics, bicycling, horseback riding, fishing, swimming, hiking and skiing. Military training is provided for further specialization in the majority of military occupational specialties applicable to the Army Air Force. In addition to class and individual instruction in such subjects as administration, clerical training, supply, teletype operation and repair, radio code, graphic arts, navigation, Link Trainer, gunnery, aircraft mechanics, automotive repair, canvas and leather work, electricity, aircraft instrument repair, machine shop practice, photography, radio operation and repair, sheet metal work, welding and woodworking, practical experience is provided by "on the job" training in these subjects.

Patients also have opportunities to enroll in numerous academic classes, shop classes and hobby groups. Through the United States Armed Forces Institute and nearby local educational institutions, many of these courses can be taken for high school and college credit. Jour-

nalism, radio broadcasting, dramatics, art, handicrafts and many other avocational activities are more than diversional in that they provide the media, along with well-rounded and complete recreation programs, for psychological adjustment and resocialization

*Psychological Readjustment and Resocialization*—A well-rounded and diversified program aimed at psychological readjustment and resocialization is of prime importance when dealing with patients returning from combat theaters. Any man returning from combat must make a great adjustment, both physically and emotionally. There is an obvious endocrine imbalance in the men who have lived in "condition red" for weeks, months, and—sometimes years! Most of these men returning from combat are fatigued to the nth degree, both physically and mentally. They must have sufficient time and understanding care during this period of human conversion from wartime to a peacetime status.

When a man enters the army he is thrown into an entirely new environment and loses contact with many of the environmental influences which have been controlling factors of his behavior. He no longer comes in close contact with many of the social institutions familiar to him with civilian life. His attitudes, habits, concepts and values during civilian life were built largely on his day-to-day associations with these familiar institutions of social life. In the army he no longer comes in close contact with these social institutions and he, therefore, is forced, because of factors in his new environment, to adopt a new set of attitudes, values, concepts and habits. When he leaves this country to enter a theater of operations, because of military necessity the distances involved cause his contacts with these stabilizing factors to become even less and as a result, those attitudes, values, habits and concepts are altered by the environment and mores of his even more restricted fields of interests.

The Army has done a splendid job in keeping the man in combat linked as closely as possible to the home ties. Our improved mail systems, communications, orientation programs, wide use of movies and similar factors have made home seem much closer to the fighting man of today than to the soldier of twenty-five years ago. But Aachen, Leyte and Bologna are not Cleveland, Pasadena and Kansas City. The environment is different, the life is different, the daily objectives are different, and it only follows that a man's thinking, behavior, concepts, ideas and values are different. When a man is wounded in combat and goes to the hospital, there is usually a temporary psychological relief, even though his wounds may be serious, due to the fact that he is alive, is out of combat for the present at least, however, new problems present themselves—problems that involve his whole future. He loses contact with the men with whom he has lived and fought in close association; the men who have to a large degree replaced his civilian associates. Regardless of the fine medical care that the casualty receives,

he is changed by his army experiences, he is a different man than he was before combat, different than he was before he was wounded. He is not necessarily a psychiatric casualty. His mental and moral fiber may be as tough or even tougher than before, but he has been out of touch with the normal activities of his normal civilian life. His attitudes, values and habits, of necessity, have changed. The restoration of these attitudes, habits, values and concepts accepted by American society must be a part of his medical treatment. By providing the soldier-patient with a laboratory of opportunity through physical reconditioning, educational-avocational pursuits and recreation he will regain those traits compatible with normal behavior patterns. By stimulating interest and motivating the patient to participate in such activities his center of interest is transferred from himself to the activities in which he is participating, with resulting adjustment and resocialization.

In an AAF convalescent hospital each patient is assigned to a personal physician who becomes his "family doctor" for the period of his hospitalization. This personal physician has a paramount place in the AAF convalescent hospital. He is the captain of the team of medical specialists, physical therapists, educators, athletic trainers, occupational therapists, social service workers, personal counsellors and vocational guidance experts, and as such, integrates their efforts in the treatment of the whole man.

The latest in physical rehabilitation technics, use of prosthetic devices, teaching of factors inherent in daily living, and skills needed by those who have physical and psychological wounds are available. All personnel have been carefully selected on the basis of experience and demonstrated ability, and many have taken special courses at the Institute for the Crippled and Disabled in New York City and at seminars conducted by the Office of the Air Surgeon and the AAF Personnel Distribution Command.

A special program has been developed in the Army Air Force for combat casualties suffering from *operational fatigue*. Pioneer work was done in this field by Grinker and his associates.<sup>11</sup> Hastings, Murray and Wright<sup>12</sup> have also added to the knowledge of this condition and its diagnosis and management. As an adjunct to this definitive psychiatric care, the AAF Convalescent Training Program, through its directed activities, has proved of value in the emotional adjustment of these patients through a program of planned physical activity, competitive sports, and nonconcentrative types of teaching. The great majority of men suffering from operational fatigue so treated are returning to duty in the Army Air Force.

**Program for the Soldier-Patient Who Is to Leave the Service**—For the men who are to be separated from the service there is, in addition to the physical reconditioning, educational training, psychological rehabilitation and resocialization opportunities, a complete program of

vocational guidance based on achievement, aptitude and functional testing and interests determined by a series of short work experience. In these short work experience under a staff of experienced vocational instructors, the patient has an opportunity to participate in a diversified educational program embracing academic subjects, commercial skills, photography, art woodworking, metal shop, welding, machine shop practice, automotive repair and a host of similar fields. The man learns not only what he likes to do but he learns what he is able to do, both in terms of ability and in terms of any handicaps he may have. He knows at the end of this period what he enjoys doing, what he is able to do and the occupations for which he possesses aptitudes. This information is correlated by a skilled vocational counsellor with the job opportunities in the field chosen, and the patient upon discharge from the hospital has a complete objective vocational profile.

At this point the community and appropriate governmental agencies, notably the Veterans Administration, must take over. It is the mission of the armed services to retain these men in the service until they have reached maximum hospital improvement, which includes all of the rehabilitative procedures that have been described, and to send these men back to the community as motivated individuals, eager and ready to take their place in the community life of a democracy. It is here that the community must take responsibility for aiding these men in living a self-supporting, self-respecting life. There is a great need for a broad educational program at the community level so that labor, industry and the relatives and friends of the returnee will understand, in some measure, his problems and how they can help him to meet them. Time, sympathetic understanding, and patience are the primary requisites.

Much has been written on the subject of the reception of the disabled soldier. If we remember that the primary rule is "IT IS THE MAN AND NOT THE DISABILITY," and we look upon him as such and use the simple rules of good manners and common sense, the problem is readily solvable. The civilian physician who is going to take over a large part of this load must aid in the broad, civilian educational program so that the civilian population will understand what happens physically and emotionally to the man returning from the wars and how to meet the problems involved.

#### POSTWAR IMPLICATIONS

The experience gained in convalescence and rehabilitation in military medicine presents new opportunities in civilian practice, postwar. Rehabilitation is not primarily a military problem. Eleven thousand men were wounded in the first ten days after "D Day." During that same period of time, over 25,000 civilians were injured in the United States in automobile accidents alone, even with gasoline rationing. It has been

estimated that there are 800,000 incapacitating accidents occurring each year in the United States. There are between 3,000,000 and 5,000,000 physically handicapped citizens in this democracy who are in need of some type of physical rehabilitation. War only focuses the spotlight of public opinion on this great national problem.

There is a great need in this country for a planned program for the patient to fill the dead space between acute illness and the ability to return to a productive occupation. A typical case in civilian life in one of our large city hospitals will illustrate this point. A 50 year old male, a high line electrician employed by a large utilities company, enters the hospital with his first cardiac breakdown. He is examined by the resident staff and the diagnosis of degenerative heart disease with decompensation is made. The diagnosis is checked by the visiting physician and proper treatment instituted. After a short period of time his heart is compensated and, following a brief period of rest, he is ready for medical discharge, usually with this advice: "Here's your medicine, take it regularly, as directed, and report back to the clinic in two weeks. You know, of course, that you will never be able to do any strenuous work and you cannot continue with your job as a high line electrician." If we stop there, the bottom drops out of this patient's world, he says to himself: "*I can't stop working, I have children in high school, my house isn't paid for, my insurance won't be paid up until next year, all I know is an electrician's work on the high line I have to work!*" And he disregards the doctor's advice—and dies. Or, he reports to his employer and asks to be retired on a pension, if he is eligible—a physical and psychological cripple, his living standards reduced 50 per cent, his buying power decreased 50 per cent—an unwilling liability to himself, his family, and to the economic structure of his country. This *must* be avoided.

The doctor alone, however, is not responsible for the solution of this problem. Labor and industry must play an active part in solving this man's problem, in salvaging him for some type of productive work within his physical capabilities, and a rehabilitation program must be set up to meet this need. If a representative of labor and industry, a skilled vocational guidance expert, could go to this man early in his hospitalization period and say: "I represent your company and labor. You are not going to be able to continue with your old job, with this type of cardiac disability, but there are fifty jobs in your company that you *can* do and we will start right now in the hospital on your retraining for a new job," the problem would soon be solved. A rehabilitation program that starts at the bedside and follows through to purposeful placement! If such a program were established, the patient would retain his self-respect and ability to be self-supporting, industry would save the required pension, labor would save a valuable workman, democracy would retain its economic level. Such a program be carried on with proper teamwork—medicine and all of its allied

sciences working with labor and industry to care for the man *as a whole*

Rehabilitation Centers, established at key points, working both on an in-patient and an out-patient basis, with direct association with hospitals and offering a program of physical and mental rehabilitation, vocational guidance, with opportunities for short-work experience and vocational testing, and, for the more severely handicapped patients, a sheltered workshop, would reclaim a large percentage of these unfortunate individuals from hopeless dependents to proud, self-sustaining individuals

The growing interest in the field of *physical medicine* opens a great, new field in rehabilitation first, physical medicine as it pertains to definitive treatment and its utilization in the diagnosis and treatment of disease, secondly, physical medicine in its broadest sense medicine in its relationship to environment, occupation, social status, and in the specific field of individual rehabilitation, utilizing as the basis the greatest physical potentialities—the potentialities of oneself, the *science* of retraining and utilization of these potentialities and the *art* of such application.

*Hospitals must be made into institutions of opportunity* The average patient in the hospital suffers but 10 per cent of the time and is bored to death the remaining 90 per cent. The hospital must take its place in the community with programs that aid the patient in his re-orientation back to normal living Occupational therapy, prevocational therapy, vocational guidance, and opportunities to broaden the patient's knowledge in his field of work, geography, languages, literature, and interesting short courses in problems of daily living, should be made a part of the hospital routine Hundreds of interesting films and slides are available through the various agencies and foundations and may be obtained by the asking They could be shown daily in the hospital wards All types of literature on foreign affairs, living in a democracy, homemaking, avocations and hobbies—all are available readily Convalescent patients with talent are an ever-available source of teachers and lecturers, and all types of civilian organizations are available to organize and implement—even take over—such programs in the community if they are shown the need for, and the potentialities of, such a program Sporadic programs of this type have already proved to be eminently successful, and if this new concept became endemic, it would have a tremendous bearing on the social life in this democracy and would greatly strengthen the keystone of medical practice—the patient-doctor relationship

Our medical schools and their faculties must meet this great challenge and include as a major part of their curricula the practical relationship of disease to economic, social and environmental factors The young physician must be made to realize that treatment of disease is only a *part* of his problem, he must also treat the *patient* The phys-



ician must know the *science* of medicine but practice the *art*. To meet the challenge of rehabilitation there must be a group of specially trained physicians who know disease and disability in its relationship to the economic, social, vocational and environmental factors, who can "captain" a team composed of specialists trained in the ancillary sciences—physical education, social service, occupational therapy, vocational guidance, psychological testing, and physical medicine. This physician would be a specialist in the field of *orthergasia*, which literally means "conditioning for normal function and adjustment." Normal function and adjustment—the goal of rehabilitation.

## BIBLIOGRAPHY

- 1 AAF Manual No. 23, Handbook of Recovery. New York, Army Air Forces, Training Aids Division, 1944.
- 2 AAF Manual No. 24, Instructors Manual for Physical Retraining. New York, Army Air Forces, Training Aids Division, 1944.
- 3 AAF Manual No. 29, Let's Walk. New York, Army Air Forces, Training Aids Division, 1945.
- 4 Van Ravenswaay, Arie C., *et al.* Clinical Aspects of Primary Atypical Pneumonia. J.A.M.A., 124:1-6 (Jan. 1) 1944.
- 5 Karpovich, Peter, *et al.* Physical Fitness Tests for Convalescents. J.A.M.A., 126(14): 873-877 (Dec. 2) 1944.
- 6 Marquardt, Gilbert, AAF Regional Station Hospital No. 1, Coral Gables, Florida. Personal communication.
- 7 Holbrook, W. Paul. The AAF Rheumatic Fever Control Program. J.A.M.A., Vol. 126, No. 2, pp. 84-87, September 9, 1944. Van Ravenswaay, Arie C. The Geographic Distribution of Hemolytic Streptococci. J.A.M.A., 126(2): 486-490 (October 21) 1944.
- 8 Proceedings of Fourth Meeting of Committee on War and Post-War Physical Rehabilitation and Reconditioning of the Baruch Committee on Physical Medicine, pp. 23-97. New York, December 14, 1944.
- 9 Dock, William. The Evil Sequelae of Complete Bed Rest. J.A.M.A., 125(16): 1083-1085 (Aug. 19) 1944. Ghormley, Ralph K. The Abuse of Rest in Bed in Orthopedic Surgery. J.A.M.A., 125(16): 1085-1087 (Aug. 19) 1944. Menninger, Karl. The Abuse of Rest in Psychiatry. J.A.M.A., 125(16): 1087-1090 (Aug. 19) 1944. Powers, John H. The Abuse of Rest as a Therapeutic Measure in Surgery. J.A.M.A., 125(16): 1079-1083 (Aug. 19) 1944.
- 10 Keys, Ancel, University of Minnesota Medical School, Minneapolis. Personal communication.
- 11 Grinker, Roy R. and Spiegel, John P. War Neuroses in North Africa. The Tunisian Campaign. New York, Josiah Macy, Jr., Foundation, 1943.
- 12 Hastings, Donald W. Wright, David G. and Glueck, Bernard C. Psychiatric Experiences of the Eighth Air Force. First Year of Combat. New York, Josiah Macy, Jr., Foundation, 1944.
- 13 Murray, John M. Psychiatric Aspects of Aviation Medicine. Psychiatry Journal of the Biology and Pathology of Interpersonal Relations, 7(1): 1-7 (Feb.) 1944.

# PSYCHIATRIC DISORDERS IN COMBAT CREWS OVERSEAS AND IN RETURNEES

LT COLONEL ROY R GRINKER  
MEDICAL CORPS, ARMY AIR FORCES

PSYCHIATRIC disturbances that result from exposure to the stress of combat we term war neuroses. In the Air Forces we use the euphemism "operational fatigue," an inheritance of peacetime aeronautics, as a convenient disguise for those who find the term "neurosis" unpalatable. This does not signify that fatigue itself is all-important as a causative factor nor that fatigue is a frequent symptom. I propose to discuss these war neuroses as they appear overseas in combat and as they are evidenced in this country among returnees. The latter group are of more interest to this audience since they closely approximate the problems that all physicians in the military service and civilian life will encounter among men who are separated from the services with medical discharges or are demobilized at the end of the war.

## PSYCHIATRIC DISTURBANCES IN WAR THEATERS

**Interacting Factors in Their Production**—To understand war neuroses one must know what internal and external factors interact in their production. They depend on the relationship of determinable forces such as the individual's psychological predisposition, his motivation and training and the morale of his unit, on which indeterminable accidental factors of stress operate.

**The Individual's Psychological Predisposition**—Obviously the reaction of the man himself under stress carries with it the coloring of his previous personality. In the Air Forces we have special psychiatric screening processes which are fairly successful in rejecting men with overt neuroses from flying training. It is not so easy to detect latent psychoneuroses or personality trends which predispose soldiers to react with war neuroses early in combat. We have found that men with psychosomatic disturbances, that is, functional visceral troubles, are almost certain to react quickly under stress with an increase in their symptoms. Compulsive-obsessive characters do not do well since their ritualistic defenses quickly break down, uncovering anxieties and depressions. Furthermore, people with depressive characters react badly to the loss of comrades and usually succumb to long-lasting melancholia. There are certain general personality types predisposing to early breakdowns, among which may be mentioned the extremely passive and dependent person constantly expecting injury to himself.

---

From the AAF Convalescent Hospital, Don Ce Sar Place, St. Petersburg Florida.

the overcompensated, tough individual who has never experienced subjective anxiety, and the schizoid person who is rather seclusive and difficult to get along with and who uses flying as a means of escape from close interpersonal relations. All these characteristics and latent tendencies are so ubiquitous that it is almost impossible to weed them out. Yet it is a matter of chance as to whether the stress will become severe enough to precipitate them into a neurosis.

Recently we have heard criticisms of the numerous rejections for psychiatric causes. It is contended that if a boy is willing, the Army should take him and through strict discipline and training make a man of him. That is a sure way to slow the war effort and ruin these boys. Army life and certainly combat is a tough business and, as I shall point out later, causes more psychological regression than growth. Psychoneurotics well adapted to some form of civilian life should be undisturbed in their adaptation or at best used only for some special army task in a particularly favorable environment. This is not a theoretical postulate but is based on practical experience.

*Motivation and Training*—Another aspect of the man himself is his motivation. There are many individuals who have strong motivation for flying but not always of a healthy type. The man who flies to get away from people, from earthly problems, or to overcompensate against his feeling of weakness on the ground, does not have a healthy motivation. This is more likely to be the initial result of strong identifications with firm but kind father figures and later with the strong and respected leader of the group.

Good training and confidence in his ability is a fortification that often protects the soldier against overwhelming anxiety while under severe stress. Lack of confidence in one's ability is often an important predisposing factor in creating excessive and uneconomical anxiety.

*Personal and Group Morale*—In modern warfare, combat is carried on in relatively small groups into which men are integrated as early as possible in training. The individual's relationship in the group as a brother to all the other men and as a son to the leader is important in establishing good morale which is the most essential protective armor against war neuroses. Morale is not the result of subscription to high-sounding ideologies or ideals of which there are relatively few in this war. That type of morale may function when one's country is attacked and one's family and friends are persecuted or tortured but even the Russians have plenty of war neuroses. But for our Army, war is a dirty business and simply a task that the soldier must finish as soon as possible in order to return home.

The best morale that can be expected depends on a good interpersonal relationship within the group. In such a setting the soldier loses his individuality, correspondingly his weaknesses, and assumes the strength and fearlessness of the group confidence in its ability and its

The leader must, of course, be strong enough to inspire con-

fidence, be fair and equitable to all his sons, and have a reasonable amount of courage himself. When morale breaks down because of disturbances in leadership, the individual quickly crystallizes out of the group solution and becomes an individual again, filled with anxiety concerning his own self-preservation. In this state he is on the way toward the development of a neurosis. The same thing happens as he leaves the group after an honorable tour of duty or is rotated home. He then becomes an individual and may even develop an anxiety state as he thinks of himself as a person in retrospect, recalling the dangers he experienced and the near catastrophes that he escaped.

*Impinging Stresses of War*—The stresses that affect an individual are those stimuli that disturb his particular character structure and break down his protective devices against anxiety. These stimuli are unpredictable and may in one case be minimal and in another be extremely harrowing. The stress is not always the danger of combat. Poor living conditions, bad food and inclement weather are among a host of other stresses that weaken the ego in its capacity to endure the anxiety stimulated by traumatic experiences. In fact, it can be stated that even more important than the effects of flak and bullets on the flier are the disturbances of close relationship with comrades in the group. The visualization of another plane being blown up, the loss of a close buddy, the loss of the soldier's ship with all the other members of the crew, are among many serious situations that create profound neurotic reactions.

From the preceding we can see that the factors of the individual's innate psychology, his training and confidence, his personal and group morale and the stresses which impinge upon him, are all important in determining the rapidity with which he succumbs to anxiety states, and their severity. From these data you could have anticipated our experiences in the theater of operations. We found that no matter how strong or normal or stable a man might be, if he had to endure stress sufficient to reach his personal threshold, he would succumb to a war neurosis. Man's threshold is variable and a stereotyped performance from each human as from an airplane engine could not be expected. Furthermore, many men with chronic anxiety states were able to endure combat without any great accretion to their subjective disturbances. These people were accustomed to anxiety and a trifle more of such distress was not too disturbing. They also often felt better when they could attribute their neurotic inner anxiety to external events. When this happened they became as normal as the others.

*Types of Neuroses Seen in Combat Crews Overseas.—Anxiety*—The most common type of war neurosis seen overseas is characterized by the subjective sensations of various quantities of free anxiety and objective signs of sympathetic overactivity. The fliers become irritable, restless and sleepless with catastrophic nightmares of battle. They develop tremors, severe startle reactions, tachycardia, loss of weight

and excessive perspiration. The anxiety state is apparent on cursory examination. There are gradations in this condition from the beginning stages in which a man shows early personality changes, loses confidence in his ability and is reluctant to go on missions. At this time he declines to talk about combat and hesitates to consult his doctor because of a misinterpretation that his condition is one of weakness or cowardice which he strenuously fights. Yet it is in this phase that therapy is most effective. The proper utilization of a rest camp for four or five days, temporary relief from combat, good food, reasonable comfort and sufficient sedation to produce sleep, often strengthen the ego sufficiently to enable it to endure more anxiety. As the process continues the individual becomes more anxious and develops phobic reactions in that he is frightened of a particular type of plane, enemy fighters, flak, bad weather, and a host of other external dangers. He may continue to fly in this stage but his abilities are markedly reduced. The pilot may become inept at the controls and handle his plane badly, or the crew members may freeze at their guns and not be able to shoot at the approaching attacking plane. Finally, the man becomes so seriously ill with anxiety that he is unable to get into the plane at all, in fact often cannot even fly as a passenger in a safe and secure transport. At this stage he must be grounded and given definitive psychiatric treatment.

*Depression*—Many soldiers develop depressions. This emotion is almost always present when a man is ill with anxiety and has to be removed from combat. He has guilt feelings and self-depreciation because his ego-ideal interprets his illness as a sign of weakness. Furthermore, many men go into a serious depression over the loss of close friends which they attribute to some omission or commission on their own part and hold themselves responsible for the tragedy. These feelings of guilt and depression are usually related to the fact that toward the lost comrade the patient has had both hostile and affectionate feelings. It is the repressed hostile feelings that are responsible for the strong feelings of guilt and depression.

*Psychosomatic States*—Psychosomatic states develop, of course, early in those who have had them in the past. However, in almost all combat neuroses some psychosomatic disturbances develop as the tolerance of the ego for anxiety decreases. The most frequent symptoms are referred to dysfunctions of the upper gastrointestinal tract. Such symptoms as nausea, vomiting, indefinite abdominal pains or severe anorexia are typical. We rarely see the disturbances in heart function that were so frequent in the last war.

*Psychosis-like Disturbances*—Another frequent type of disturbance occurs in combat and resembles certain psychoses in that the individual's ego has lost its power to discriminate dangerous from safe reality. The whole world becomes a hostile dangerous place to which he constantly reacts with apprehension. Or he may regress into an

apathetic, dull, almost schizophrenic state. He may become paranoid and believe that all people including his friends and comrades are hostile to him. There may occur a severe dissociation of his personality in that the memory of a severely traumatic situation or the emotional concomitants are repressed into his unconscious, causing a partial amnesia.

**Prophylaxis**—The prophylactic treatment against war neuroses includes successful selections of men and their maintenance with proper treatment by the flight surgeon. The most important part of prophylaxis is, of course, to maintain a good group morale which is a function of command assisted by advice from the medical officer. The early treatment of neurosis is rest and psychological support to strengthen the ego forces which repress anxiety, and this is successful only when physical fatigue and psychological exhaustion are important factors in the etiology. When these methods are not successful the flier must be grounded and referred for definite psychiatric care. For the severe cases recovery cannot be accomplished in a theater of operations in a brief time. Therefore, most of these men are sent to the United States for rehabilitation. Once a man has developed a definite neurosis rehabilitation overseas is successful only in bringing men back to a condition in which they can return to reclassified duty. Only rarely is it possible to send them back to combat.

#### PSYCHIATRIC DISORDERS IN RETURNEES

**Etiology**—The Army Air Forces have made provisions in this country for the adequate treatment of returned combat troops suffering from "operational fatigue." However, the majority of admissions to the hospital are not men who returned home with war neuroses but those who developed signs of sickness after completing a full tour of duty. Their symptoms developed or increased after release from combat, during their furloughs or while anticipating reassignment. There are a number of possible explanations for this fact. Some men had mild neuroses which they held under control as long as there was a purpose for so doing, but after completion of combat their ability to suppress symptoms failed. Anticipation of returning to combat after furloughs may be the last straw of anxiety added to the load which the ego has already had to bear so that the man develops a neurosis. It sometimes happens that the weakened individual is disturbed because he had returned to a home situation which is unsettled and conflictual to him as it has been in the past. Finally sometimes the soldier has been so changed as a result of his combat experiences that he cannot adjust to living in even the most favorable environments at home or in the United States. All these factors have their share in the production of war neurosis in returnees. We frequently say that the neuroses produced by combat are the result of abnormally severe stresses impinging upon a relatively normal personality. We can reverse this axiom

and state that war neuroses that develop at home are the result of the difficulties of a changed personality to adapt itself to relatively normal environmental circumstances. It is this type of patient that we all will have to treat long after the war has ended.

**Symptoms**—Among the most frequent symptoms of "operational fatigue" in returnees are restlessness, irritability or lethargy, insomnia, battle dreams, loss of weight, signs of sympathetic overactivity, alcoholism, startle reactions, subjective anxiety and depression, anorexia, upper abdominal pain, nausea and vomiting, aggressive and hostile behavior, paranoid reactions and mental confusion. These are the major symptoms of war neuroses developed overseas, during or after combat, as well as the neuroses that manifest themselves in returnees. In the latter, such symptoms are usually milder.

**Classification**—Almost every returned combat veteran has a certain degree of physiological and psychological disturbance, but these unwind or uncoil within the course of relatively few weeks time. The abnormal reactions persist despite time, rest or any other procedure except definitive psychiatric care. No one symptom or group of symptoms is characteristic of a particular syndrome, yet we can classify people as to the leading psychological trend which they reveal on closer analysis of their problems. We are able to divide them in spite of considerable overlapping, into (1) the passive-dependent reactions, (2) the hostile-aggressive reactions, (3) the depressions, (4) the psychosomatic reactions, (5) the psychotic-like states.

**Passive-Dependent Reactions**—The passive-dependent individuals who form the largest number of our sickest returned soldiers may express this trend overtly and in doing so they resemble small children. They long to get home to mother or wife and be taken care of as a baby. They are unable to withstand any deprivation and complain that even the best treatment is restricting. Under pentothal they cry and sob as they relate the terrible things that have happened to them and how they have done all that they possibly can and now it is time for them to go home. In the purest form these people have no self-respecting remnant to their egos that can cooperate therapeutically. However, there are other types in which there is some defense against this regressed dependency. These individuals may express their needs only by excessive drinking. Some of them talk about going home to take care of their parents or families, turning around their great needs as if it were others who needed help and attention. Occasionally we find an overcompensated individual who aggressively attempts to deny his dependency. Some of these boys seek for mother substitutes in rapidly contracted marriages. In many there are associated gastrointestinal symptoms. In all of them there is considerable hostility directed against the Army. The Army represents the cruel father who will not let the boy return home to mama. But in addition, the hostility that was well repressed in the group situation in combat now is released

and no longer displaced toward the enemy but toward the authoritative figures that are responsible for all the bad happenings in combat. It is like a little child who stumbles over a chair and hurts itself, looks up and accuses the first human adult figure with the cry "see what you made me do!"

The passive and dependent group is a mixture of persons whose personalities had reached varying degrees of maturity. Many had never attained any great degree of independence, while others have regressed under the impact of stress. The latter offer the best prognosis for recovery. Many youngsters who had not had time in life prior to combat to attain any ego confidence that accompanies maturity, may use their achievement in retrospect in subsequent therapy. Some of these dependent youngsters suffer from what we have called the *syndrome of ego depletion*. They have given out in independent and aggressive behavior far beyond their capacities, without replenishment to them through affection or love. In this state of psychological bankruptcy they need to rebuild a reservoir of ego strength through the accretion and replenishing effect of being loved. In so doing they resemble children in a stage of development when such an overwhelming intaking process is normal for their chronological ages—children who want everything, who want love and attention, but themselves love only those who give, and turn with rage on those who deprive.

It is this dependent yearning that constitutes our greatest social danger from the veterans of combat who demand rewards as symbols of gratification. Such rewards must be kept up perpetually, for dependent hungers are insatiable. The large numbers of these personalities bring to us a huge therapeutic problem.

*Hostile-Aggressive Reactions*—The hostile, aggressive individuals may be sullen and negativistic. They are unruly and incapable of obeying the minor discipline of the hospital. Under the influence of alcohol they become wildly aggressive, attacking civilians and fellow soldiers who have not been overseas. Often this behavior compensates against a passive trend. Sometimes it is a means of attaining the attention of the doctors and nurses around them. Often enough it is a need to receive punishment because of guilt feelings related to happenings in combat for which they hold themselves responsible. The majority, however, are extremely aggressive because the goal of their hostilities has been taken away from them. They are no longer able to express their aggressions against the enemy. Their personalities regressed by incorporation into groups and through the stress of combat have lost their internalized ego ideals and there are no inward checks against aggression. The only forces counteracting these trends are external. In the normal course of events the personal and civilized standards of conduct are soon reestablished. When such ego-ideals were originally weak there is a lengthy period of unsocialized conduct often becoming pathological. Correspondingly we have observed that not kindness



and leniency but a temporary firm and strict attitude is productive of the greatest amelioration of this hostile reaction, succeeding far better than persuasion or rational arguments

*Psychosomatic Reactions*—Psychosomatic symptoms are for the most part related to the upper gastrointestinal tract. Diffuse pain in the abdomen, pain related to food taking, nausea, vomiting and anorexia are among the most frequent complaints, with no positive x-ray or laboratory findings. Most of these patients are only able to ingest milk, vomiting all solid food. They all have considerable anxiety but attribute this emotion to their symptoms. Analysis of the underlying trends also reveals that these patients are not at all conscious of the meaning of their symptoms even though anxiety has spilled into consciousness. The symptoms are indicative of a severe regression to an infantile level, the trends of which cannot reach the level of thought, verbalization or somatic behavior. Some patients express their great need for love and affection by increased activity of the primary intaking organ, the stomach, whose filling the infant connotes with satisfaction. Thus it is only milk that can be retained, an essentially infantile food. Others who feel as if there are weights on their stomachs have a great quantity of repressed hostility which can only be expressed at a low visceral level and they often vomit as the child does so readily, in an infantile way of expressing aggression. When the effect which is part of such "lower level" emotional expressions is made conscious through the use of pentothal narcosynthesis, the symptoms rapidly disappear, indicating their negative relationship to conscious feelings.

*Depression*—Depressions are usually related to a personal loss. This may be a superior officer, buddy, fellow crew member or some person to whom the patient was closely attached or identified. The soldier berates himself and considers he is responsible for the death of his friend either directly or indirectly. The mere fact of leaving the group, overseas in combat and returning home to benefit from life in the United States with all its advantages and luxuries is sufficient to produce depression in almost every soldier but it normally subsides in a few weeks. In every case the underlying emotion that has been unrecognized is a negative feeling toward the object toward whom the patient feels guilty.

*Psychotic-like States*—The psychotic states are temporary and benign and not frequent in returnees since recovery is usually effected by the time they reach the United States. Frequently there is a severe ego breakdown in ability to differentiate and discriminate safe from dangerous reality. Often the person cannot discriminate between the safe reality of here and now, thinking that he is back in combat and reacts accordingly with apprehension and startle or violent aggression. This is particularly true when he closes his eyes or during the transition periods between waking and sleeping.

**Progressive Nature of These States**—It is apparent that all these states never clearly defined as separate syndromes, are regressive in nature. In some the ego itself has regressed and the resultant personality resembles that of a small child. In others the psychological trends arising from dynamic forces within the depths of the individual overcome the ego's efforts to maintain a mature attitude and produce partial patterns of childish behavior.

The immediate source of the regression is the external weight of severe traumatic situations which the soldier experiences overseas in combat. The degree of preparedness for regression and the pattern adopted has been laid down by the previous personality structure of the individual. Acting on this personality, the severe blows of psychological and physical trauma are temporarily buffeted by the strength which the ego borrows from the group. Once the individual crystallizes out of the group, he becomes dependent on the strength of his own ego and the stability of his ego ideals. These are badly weakened by his initial abandonment of them when he enters the group followed by the catastrophic effects of battle. The external forces of a hostile dangerous world leave no recourse for gratification except phantasy. The ego returns to the only safe and secure position that it has known, its childhood past. In that state it is maintained in dream or phantasy of the past or hope and longing for the future, even enduring further trauma for the ethereal promise of a magical and unrealistic reconstructed future life—a fairy land of dreams unfortunately never to come true.

The soldier then returns home and finds that living out his regressed desires is sadly frustrated. He is a man and a hero and cannot climb on mother's lap, nor can he ever find in reality the complete satisfaction of even partial wishes. Civilians extol him as a great man and the Army insists that he continue his responsibilities in base duties within the United States where restrictions are greater than on overseas duty. Frustrated, his personality is then in conflict with reality. Or an intrapsychic conflict develops between a part of his personality that wishes to deny the regression and the part that wishes to be gratified. The result is anxiety and all the symptoms of a neurosis identical to that which occurs overseas.

**Treatment**—The treatment is, of course, psychotherapy of a type that first uncovers the essential problems. Persuasion, forcing and exhortation are palliative and largely unsuccessful except to cover up the basic problems. Rational psychotherapy consists in uncovering the conflict whether it be between the patient's ego and reality or an intrapsychic struggle. With plenty of time this can be done by psychiatric interviews. The pressure of great numbers requires shorter methods, hence pentothal is advantageous. In a state of partial narcosis the patient is able to abreact his hidden emotions and synthesize them within his conscious ego, hence we call the

method *narcosynthesis*. After the heavy unconscious loads are released the patient knows what powerful drives he has to deal with and with what uneconomical methods his ego has attempted the task. Supported by the therapist and identified with his strength, the patient can tackle the problem of reeducation. Each type of case presents a different therapeutic problem and the most that we can accomplish in a short time is to relieve the disturbances that have developed as the result of combat or start the patient on his road to recovery. When we encounter a severe psychoneurosis or personality disturbance that has antedated combat and been made worse by it, we can often help the patient understand his previous patterns but seldom effect any profound change.

A comprehensive program of planned recreation, physical activity of the competitive type, and nonconcentrative types of vocational and avocational teaching with a definite purpose is a valuable addition as adjunctive therapy.

The results are most gratifying in that 95 per cent of our officer patients and 80 per cent of our enlisted men are returned to full duty. The difference in these figures is based on the fact that officer selection is much more thorough and careful, hence chronic psychoneuroses or lifelong pathologically crippled characters are fewer and officer motivation for continuing duty and for recovery is higher.

#### POSTDISCHARGE PROBLEMS

We are not concerned with erasing the effects of combat only to salvage manpower for the war effort. We are also concerned with attempting to send men back to civilian life as independent as possible and as free from regressed trends as can be accomplished. Giving a man a medical discharge invites him to descend the toboggan of dependency, since perpetual veterans' medical care and pensions are his for the asking.

The problem posed by large numbers of soldiers who will return to civilian life on demobilization with tendencies toward regression and susceptibility to react neurotically to rather mild, new traumatic situations is one that will have to be met by all physicians. Every doctor will need to bear in mind the psychological background of the veteran who develops psychosomatic disturbances and other more obviously psychiatric disorders and must be aware of how combat experiences have prepared these men for medical and personality disturbances. The prognosis for good recovery should be as high in civilian life as in the Army, provided that rational and adequate methods of therapy are utilized. There are not enough psychiatrists to carry the load successfully and probably never will be. Thousands of physicians will have to learn the technic of brief psychotherapy and of group psychotherapy. That this is possible has been shown by our success in training general medical officers as assistant psychiatrists.

They have been able to function admirably and, frankly, better than many psychiatrists who are bound up with only diagnostic outlooks. New clinics will have to be opened all over the country. Social workers and clinical psychologists will be required as therapeutic assistants. Social technic will have to be employed based on knowledge of the individual psychological trends but streamlined to mass needs in order to reincorporate these individuals into democratic civilian groups.

The task is tremendous but it must not fail because the consequences would be a profound disturbance of our social structure, since regressed personalities are followers, equally susceptible to leadership by demagogues, psychopathic characters and destructive personalities. Postwar problems of the demobilized combat veteran require cooperative endeavor of all those concerned with human beings, but occupying the most important position with the chance to do the greatest good at the earliest time is the general practitioner, the family doctor.

# PSYCHOSOMATIC ASPECTS OF REHABILITATION

MAJOR ALBERT A. ROSNER

MEDICAL CORPS, ARMY OF THE UNITED STATES

THE effective handling of the returned veteran soldier will demand much of this country's skill and ingenuity. A nation utterly unprepared for war, yet capable upon attack of miraculous conversion and successful counterattack, is capable in no less a measure of devoting its whole resources to the reconversion of its tempered soldiers to temperate civilians. One need not underestimate the immensity of the problem. Our armies are large and have wandered deep and far in the mires of war. The war has been grim, and mutilation is no less a prerogative of the mind than it is of the body. Wounded or not, the soldier returning is something other than the soldier having gone.

The soldier wounded poses special problems that are not, in the usually accepted sense, altogether medical or surgical. It is apparent, for example, that a soldier-patient, emancipated by army service from real economic want, and looking forward with trepidation to a return to the competitive economic game, regards somewhat dubiously the healing of his wounds. Anxiety compromises body function and conditions attitude. This attitude may be subject to influences well beyond the reach but not the understanding of his medical administrators. It is apparent that this soldier requires more than skillful attention to his immediate health problem in preparation for his future. The premature discharge of such a soldier, without resolution of his personal conflicts, might prove a costly error, not only for him but for his community. This man's mental attitude as he steps off the train at his home station is a matter of deep and immediate concern to his parents, fiancée, pastor, employer, neighbor and constabulary.

The physician who blinds himself to these social qualities and obligations overlooks matters of deep medical significance. It is his responsibility to view and treat his patient not only as a disabled soldier but as a man with conflict situations that might require attention. He must recognize that there are forces at work which, if poorly channeled, might spell lifelong dependency of an anxiety-ridden postwar casualty upon the government pension list. The physician must recognize the anxiety problem, however disguised, when first it appears on the stage. He must understand why soldiers, who have lived long and intimately with fear, find themselves burdened with its poor relation, anxiety. He must understand that forces which mitigate toward good or bad vegetative function are of direct consequence in the prognosis of any given patient. Knowing these things, the physician is in a position to lend a firm and tactful hand in the early resolution of this kind

of problem which otherwise, in time, shows a disconcerting tendency to dominate the medical situation. He is obliged in other words, to appreciate the soldier problem as a whole, for all that the soldier was, is and hopes to be are matters inextricably bound with his patient's progress.

The reduction of the personality equation to terms of the immediate medical situation should be the first requisite of any therapeutic program. This is not easily done, though some striking advances have been made along these lines.<sup>12 13 31 46</sup> It has been shown, for example, that certain personality patterns and disease susceptibility are physiologically bound and that dynamic influences imposed by environmental and emotional tensions are prepotent as symptom-producers through vegetative-nervous or hormonal influences, and that treatment aimed at the resolution of anxiety may successfully mediate in chronic illness otherwise considered hopeless. These are no mean accomplishments and bear directly upon the problem of rehabilitation.

The way has been opened by these demonstrations for more complete understanding of illness as a three dimensional problem of very wide scope wherein psychodynamic and physiological elements coexist as prime movers in the course and quality of illness. The therapeutic barriers encountered in war disease and war injury<sup>20</sup> emphasize the need for this kind of thinking. Resistance to treatment and chronicity are indigenous to military medicine where the battle of instincts looms stark naked and unadorned and where the element of secondary gain through illness not infrequently displays itself in peculiarly brazen style. The high incidence of so-called psychosomatic illness in the presence of readily apparent and well-defined conflict situations<sup>11 22, 24 25 32, 35 38 40 45</sup> reiterates the old argument raised by Socrates who, upon returning from the Thracian campaign, insisted that Greek medicine had much to learn from the enemy of psychological insight in disease.

#### INCIDENCE OF PSYCHOSOMATIC DISORDER

Present-day standards of medical reporting do not permit satisfactory estimation of incidence of so-called psychosomatic illness. The logical method of making such a determination demands cooperative project-studies by representative internists, surgeons, psychiatrists, and other specialists. Combined studies of this type are rare. Exhaustive studies by Dunbar<sup>18</sup> indicate that 80 per cent of routine civilian hospital cases are burdened with psychological problems that bear directly upon the course and progress of their illness. Seventy-five per cent of the difficulties of convalescence, according to Strecker, have their primary origin not in the body but in the mind of the patient.<sup>42</sup>

The prevalence of disease in the armed service influenced by emotional factors may be judged by the incidence of "neurocirculatory asthenia" in the last world war<sup>14</sup> and the occurrence of gastrointestinal

disease reported by so many sources in this war<sup>15, 16, 17, 18, 44</sup> Seventy thousand soldiers in the British Army were observed for cardiac disease between 1914-18, only one sixth of this group were shown to have undisputed focal disease of the heart, of the remainder, classified as having the "effort syndrome," 44,000 were pensioned. Today, for reasons unknown, the gastrointestinal tract has replaced the heart as an invalid-producer. Described as the largest single type of disease among the military sick, gastrointestinal illness was responsible for many hospital admissions in the British Army.<sup>44</sup> The history of neurocirculatory asthenia since DaCosta's time and especially during the two decades following the first world war, substantiates without much question the major role of the psychogenic element in the causation of the syndrome. From these studies, neurocirculatory asthenia emerges primarily as a psychological disorder in many of the cases,<sup>14</sup> leaving a good deal of doubt as to whether the term is warranted at all as an alternative for psychoneurosis.

The extent to which known medical conditions other than neurocirculatory asthenia may emerge as expressions of psychological conflict and as sensations of inward excitement is problematical. A point of practical importance, however, is the fact that military hospital populations show a high incidence of disturbed vegetative function as shown, for example, by the prevalence of syncopal phenomena and nonfocal gastrointestinal or cardiovascular conditions. Studies of palmar sweating<sup>40</sup> in these patients confirms the readily demonstrated fact that the anxiety factor as a least common denominator is largely responsible for symptoms which not infrequently masquerade as organ-connected disease. If the study of the mind-body relationship has succeeded in providing insight as to how this transformation is accomplished, psychosomatology will have contributed greatly to the problems of convalescence and rehabilitation.

#### PSYCHOSOMATIC PRINCIPLES

The investigation of the dynamic influence of the nervous system upon end organs and the antidromic effects of somatic disease upon the personality is not new, and in the course of time has reached a fairly high level of evolutionary development. The anatomical and physiological foundations of psychosomatology are substantial, and experimental efforts in the clinic and in the laboratory, especially in the field of conditioned reflex, vindicate its claim as a sound and orderly methodology. The basic premise that intrapersonal tensions may be translated into symptoms readily appreciated by the patient and recognizable as true physiological events by the physician is supported by evidence from many sources.

As one observes a psychotic patient succumb to the hypoglycemic effects of insulin treatment a regular succession of neurological events is unfolded each stage of deepening coma featuring more and more primitive types of reflex behavior. The susceptibility of cortical cells, especially those of recent phylogenetic origin, to anoxic influences is well demonstrated by this interesting experiment in nature, an experiment which recapitulates some prime neurological principles laid down long ago by Hughlings Jackson, Wilson Henry Head, Sherrington and others. The process of gradual and progressive dissolution of cortical function effected by insulin induced anoxemia is reciprocated by the appearance of reflex mechanisms ordinarily maintained in tonic inhibitory balance by upper segmental cortical influences. Descending levels of consciousness are accompanied by a descending physiological gradient that roughly recapitulates, in reverse, the development of the human brain.

During early stages of insulin shock, delirious manifestations predominate, characterized by affective lability, uninhibited behavior, archaic speech formulae, motor excitement and recession from reality. As the regression process continues and telencephalic influences recede further and farther into the background other cortical release phenomena appear in the form of choreiform and athetoid fragments, representing the phylogenetically older striatal motor system. Sucking movements of the lips, facial grimacing, rigidity and tremor are common. Eventually, if the process is permitted to continue, a condition analogous to decerebrate rigidity supervenes wherein very primitive labyrinthian and neck reflexes, ordinarily deeply buried, are uncovered. The patient in this stage manifests evidences of great disorganization of vegetative function—cardiac abnormalities, hyperhidrosis, respiratory irregularities and poikilothermia are prominent. With the administration of glucose, the physiological trend of events is reversed in greater or lesser detail, and coma emerges into gradually increasing awareness. Full recovery of intellectual grasp and capacity is last to appear frequently long after a relative state of consciousness has obtained.

What does one learn from observing this sequence of physiological events? First, the Sherringtonian principle of segmental domination of the central nervous system—i.e., the successive layer-by-layer domination of lower by higher motor centers—is well illustrated. Second, the whole complicated process of neurophysiological regression is shown to be completely reversible. One gathers moreover that the diencephalon, and in particular the head nuclei of the autonomic nervous system in the hypothalamus, like other elements of the central nervous system, are influenced by controlling mechanisms higher in the neurogenetic segmental scale.

This dissociation principle is also observed in the function of the hypothalamus. Cell groups in the anterior part of the hypothalamus and in the region of the tuber cinereum are considered the head nuclei of the parasympathetic system, whereas other ocellar elements in the posterior parts of the hypothalamus are generally considered the chief centers of sympathetic function. These and other nuclei of the lower part of the diencephalon are intimately bound with controlling mechanism governing the basic vital functions of life—metabolism, temperature, sleep, water balance, gastric motility, ovulation, genital function. Primitive reactions of defense or attack are mediated here and are expressed largely through the autonomic nervous system as visceral or somatic change. Emotional states, such as rage reactions with concomitant peripheral effects, are noted when influence of higher cortical centers is removed by decortication or more spe-



cifically, when fibers passing from the posterior sympathetic nuclei to the cortex are severed<sup>2, 3, 20</sup> Like other elements of the central nervous segmental hierarchy, sympathetic and parasympathetic affects are magnified when restraining influences of higher centers are removed<sup>3, 4</sup> The significance of such dissociated function from the point of view of human emotions and its visceral and somatic counterparts cannot be overestimated This is especially true of anxiety syndromes in which distorted and exaggerated fear reactions interfering with normal, purposeful activity operate as dissociated physiological fragments

### THE NEUROPHYSIOLOGY OF EMOTIONS

Emotion has been defined as "a highly integrated conative, cognitive and affective-somatic reaction in which not only the central nervous system but the entire organism functions as a psychobiologic whole"<sup>28</sup> Emotions are thus conceived as polyphasic composites blending autonomic, cortical and hormonal effects The structural identity of emotions is indicated by the fact that they appear to follow the general laws of segmental integration—they are cortically inhibited, they are activated and exaggerated by cortical release Their physiological specificity is further adducted from the fact that they may be propagated *de novo* in the human by mechanical stimulation during operative exposure through the third ventricle Such stimulation may give rise to crude exaggerated emotional effects of great dramatic intensity<sup>21</sup> Interestingly enough, feeling tones of more subtle character with greater psychic values, as described by Henry Head, may be further focalized like any other neurological symptom, by referral either to the right or to the left side of the body in accordance with the position of the responsible thalamic lesion

Heavily charged emotional states of great psychiatric complexity may prevail when physiological dissociation between supra- and infra-segmental structures occur During epileptic crises<sup>6, 7</sup> or the oculogyric crises of epidemic encephalitis<sup>33, 34</sup> obsessive-compulsive behavior, varieties of forced thinking, delusional patterns, and even projection-mechanisms make their appearance as highly integrated mental symptoms functionally bound to primitive emotional states of subcortical origin At the time they are observed, these dissociated states may approximate classical neurotic or psychotic syndromes They represent dissociated physiological entities capable of reactivation as unit structures and have been termed *unit reaction states*<sup>34</sup> The psychopathological configurations that are reactivated *en bloc* during spells are dissociated unit structures delineating specific elements of ideation, emotion, and motility

The identification of emotional elements of this type, possessing definite psychomotor and physiological identity, and capable of forcefully influencing the over-all reactivity of the individual, facilitates the understanding of unconscious mechanisms and their relationship to human behavior The preservation in the brain, intact, beyond the  
 of consciousness, of unit reaction states or complexes, capable

of catastrophic reactivation as physiologically effective units, agrees entirely with psychiatric conceptions of repression and emotional release. Epileptic or oculogyric crises are not the only trigger mechanisms effecting such release. Psychoanalysis demonstrates this principle routinely. Suggestion by hypnosis may not only implant an unconscious symptom-producing complex, but may accomplish its catharsis with complete relief of experimentally produced symptoms.<sup>6 10 10</sup> Of equal interest from the psychosomatic standpoint is the fact that experimentally produced anxiety states so induced are accompanied by a full complement of physiological effects translated into cardiovascular and vasomotor symptoms, these, too, disappear with the resolution of the underlying tension state.<sup>10</sup>

Following the general principle of dissociated function, emotions like fear, anger or anxiety may be experienced with greater or lesser emphasis on peripheral autonomic gear. Conspicuous somatic effects may dominate the scene.

Sheehan, for example, reports a patient with Raynaud's disease who when aroused to a state of anxiety, by the appearance of her physician, repeatedly displayed vasospastic effects.<sup>20</sup> One patient, studied at the Neurological Institute, suffered attacks of this sort as a consistent preliminary to submerging her hands in cold water. Subjectively experienced anxiety or fear reactions, on the other hand may find their origin in the soma. Kasanin's patient, capable of enacting her anxiety state with an odd feeling of affectless detachment, was discovered to have a medullary adrenal tumor which when removed resulted in the complete cessation of symptoms.<sup>21</sup> Injections of adrenalin alone in susceptible individuals may give rise to acute anxiety reactions.

Whether tachycardia, hyperpnea or anxiety dominates, in any given case is a physiological accident that has little bearing on the fundamental fact that emotional states are multidimensional mechanisms that involve both central and peripheral mediators and end organs—the affect system, chemically and anatomically bound, is wholly reciprocal in function.

Anxiety equivalents, expressed in the somatic language of the body as pathological alterations in tonus, secretion and circulation may camouflage the upper segmental sources of the disturbance. *In this sense they may be regarded as autonomic varieties of false-localizing neurological signs.* There is a profusion of evidence that identifies the hypothalamus rather than the stomach as the original focus of peptic ulcer.<sup>8, 9 20 41</sup> Affect-loaded psychic influences, especially those heavily invested with aggression and hostility bear down upon the autonomic head nuclei of the hypothalamus prevailing upon the final common thoracolumbar autonomic path to effect focal changes in the stomach mucosa as well as generalized adrenergic effects elsewhere in the somatic system. Cholinergic reaction-syndromes on the other hand, follow successful domination by suprasegmental impulses of the craniosacral parasympathetic apparatus.

This method of translating disturbed physiological relationships at high levels into altered function at lower levels, whatever the mode of transmission, permits the designation of psychosomatic symptoms as projected emotional effects. Any factor that compromises the tonic inhibitory influence of the cortex upon the lower centers permits the emergence of physiological reflexes or complexes of a lower phylogenetic order. Regression to more primitive reaction-patterns and potentiation, characteristic of release phenomena, explains the unreasonable intensity of fear, anger or anxiety displayed by the decorticate animal, the hypoglycemic human, the anoxic aviator,<sup>1</sup> the "shell shocked" soldier, the unit reaction state, and the overinhibited, overconditioned animal or human. Whatever disagreement obtains as to the cause of dissociated function as it applies to the human, there is ample evidence that dissociation responses of this order may be reversible and capable of resolution upon reestablishment, by whatever means, of normal intersegmental relationships. The prognosis in any given case, irrespective of the adapted pattern, depends upon the degree of susceptibility to dissociation, it is this susceptibility that measures the psychosomatic distinctions between one personality type and another.

#### THE PERSONALITY PATTERNS

It is not by accident that the conglomeration that spells schizoid personality also designates its biological fault. If one may predicate on the basis of the evidence that schizophrenia is a disease characterized by dissociation of function, then one is justified in assuming that individuals predisposed to schizophrenia are predisposed to its morbid physiology. The disposition of certain personality types to develop characteristic reaction-patterns has a practical bearing on questions of diagnosis and prognosis and has brought about the formulation of descriptive personality panels. For the most part, however, these labels designate the effect, i.e., *introverted* or *extroverted* personality, rather than the cause. One gains insufficient insight as to the basic nature of the presenting symptoms upon discovering that this patient possesses *hysteroid* or that patient *cycloid* personality features. The common ground for an acceptable system of personality identification must satisfy specific requirements demanded by our knowledge of physiology. It is the susceptibility to dissociated affects and the common affectivity of such dissociation that forms the meeting ground for all grades of psychobiological conflict. Panels formulated in accordance with such principles indicate a prevailing correspondence between somatic syndrome and personality profile.<sup>13, 46</sup> Elaborate statistical and medicopsychiatric studies have already pointed the way to better psychophysiological understanding in all branches of surgical and medical practice.

## THE LATER FATE OF ANXIETY

Rehabilitation demands a three-dimensional approach to medical and surgical problems that takes due account of conflictual and emotional elements of the personality situation. War breeds psychological regression. The normal inhibitory forces exerted by the cortex in the presence of long-continued exposure to the fear and anxiety of the war situation become attenuated, especially in the presence of chronic fatigue, and symptoms of the regressive type appear. The adaptation of more primitive reflexological modes of behavior, with its dulling of the discriminative capacity, may serve a useful purpose as a defense against anxiety.<sup>30</sup> Carried further, however, the regression process uncovers reaction-patterns inimicable to the health and the safety of either the soldier or his organization and the soldier becomes a neuro-psychiatric casualty.

This process of psychological reversal accounts for the hyperexcitability, lack of emotional control, inability to select and discriminate between stimuli, and the state of total reactivity to innocuous stimuli that forms the core of soldier neuroses.<sup>35 41</sup> Exaggerated vegetative effects are reflected in the gastrointestinal, cardiovascular and respiratory systems as diarrhea, anorexia, hyperemesis, palpitation, tachypnea and the like, sympatheticotonic effects predominating. Anxiety engendered during prolonged exposure to the chaos or monotony of military life may emerge, like certain viruses, only when circumstances are propitious. The persistence of anxiety and its bound autonomic elements, long after precipitating circumstances are gone, poses real therapeutic obstacles.<sup>35 36</sup> Any program aimed at complete restitution of the health of the soldier must anticipate a high incidence of anxiety and the propensity of anxiety elements to invest illness, especially chronic illness, with supernatant properties purely psychogenic. In its broader aspects the later fate of war-engendered anxiety is an economic as well as a medical issue.

## PRINCIPLES OF TREATMENT

Lowered threshold to fear is matched by lowered threshold to suggestion. Neglect of this potentially dangerous susceptibility may enormously complicate the healing program. One can only speculate on how many invalids have been made, not on the battlefield but in the safe environs of the hospital, by overattention to somatic ailments whose tenacity, if not origin, stems from anxiety sources. Overzealous treatment of the organ at the expense of the personality may in part have contributed to the rising incidence of psychosomatic problems.<sup>23</sup> Even the presence of serious somatic illness is no contraindication to judicious avoidance of overconcern on the part of the physician. He must decline the bait of latent anxiety and its promise to the patient of secondary gain.

The prevailing state of psychological disequilibrium that marks

the convalescent soldier demands a reevaluation of some basic principles of medical therapy. Symptomatic treatment can be dangerously provocative. The abuse of bed rest<sup>43</sup> in a cardiac patient, for example, may reverse the process of recovery and reduce exercise tolerance to zero. Aside from deleterious psychological effects, ill-considered rest, in the orthopedic patient, may be responsible for bone atrophy, muscle wasting or embolism. In any patient subject to the restraining influence of the bed, constipation, cathartic habituation, and vasomotor atonia are rest-induced sequelae that, as anxiety producers, are better anticipated and avoided than regretted in retrospect.

The use of narcotics, like rest, must be reevaluated in the rehabilitation process. Though the selective intravenous use of barbiturate derivatives has a proven value, prolonged dependence upon sedatives may challenge recovery. The sedative habit is only one manifestation of treatment resistance unconsciously adapted by the convalescent patient. Less likely to become tools of latent neurotic tendencies are the belladonna derivatives, benzedrine and ergotamine, effective in the treatment of combat-induced neurovegetative disorders<sup>24</sup> that tend to persist long after other elements of the medical situation are gone. Pharmacodynamic effects, however, will never resolve psychologically determined symptoms. This is a psychiatric responsibility to be shared by all members of the medical faculty.

The neuropsychiatrist cannot dissociate himself from problems of convalescence, that psychosomatic complex—the healing human body—invites active neuropsychiatric attention<sup>36</sup> and affords the neuropsychiatrist an opportunity to provide a fuller measure of appreciation of the psychodynamics and true personality behind the symptom. His experience may be of assistance in the formation and execution of interesting, progressive, day-by-day convalescent schedules for patients. Occupational therapy, like any other form of therapy, must be exactly and scientifically prescribed. The rehabilitation of the soldier, irrespective of diagnosis, should begin at the earliest possible moment, should be modified according to his progress, and should either be completed or well under way before he is passed on from the hospital to succeeding agencies. The deployment of mental hygiene units in transition and supervisory roles<sup>37</sup> will anticipate the uncertainty and indecision incident to hospital discharge and facilitate the substitution of the civilian for the military way of life.

A normal balance between thinking and feeling is seriously jeopardized by war experience. Primordial fear, unbound, after centuries of painstaking repression, destroys this equilibrium. The reconquest of fear and its equivalents is the common task of the moment, it is here that psychosomatic understanding provides its full and special share of hope and promise.

## BIBLIOGRAPHY

- 1 Barach A Impairment of Emotional Control Produced Both by Lowering and Raising the Oxygen Pressure in the Atmosphere *VI CLIN NORTH AMERICA* 28 704 (May) 1944
- 2 Bard P A Diencephalic Mechanism for the Expression of Rage with Special Reference to the Sympathetic Nervous System *Am J Physiol.*, 84 490 1928
- 3 Bard P The Central Representation of the Sympathetic Nervous System *Arch Neurol & Psychiat.*, 22 730 1929
- 4 Brickner R M Certain Characteristics of the Cortical Influence over the Sympathetic Nervous System in Man *J Nerv & Ment. Dis.*, 71 689 1930
- 5 Brickner R M and Kubie, L. S Miniature Psychotic Storm Produced by Superego Conflict over Simple Post Hypnotic Suggestion *Psychoanalvt Quart.*, 5 467 (Oct.) 1936
- 6 Brickner R M., Rosner A A and Munro R Physiological Aspects of the Obsessive State *Psychosom Med.*, 2 369 (Oct) 1940
- 7 Brickner R M., Rosner A A and Yaskin H Evidences Concerning the Neural Groundwork Underlying Certain Behavior Patterns *Psychosom Med.*, 5 20 (Jan) 1943
- 8 Cannon W B Importance of Emotional Attitudes for Good Digestion *Tr Am Dietet. A.*, 15 333 (May) 1939
- 9 Cushing Harvey Peptic Ulcers and the Interbrain *Surg Gynec & Obst.*, 55 1 (July) 1932
- 10 Deutsch F and Kauf E. Über die Ursachen der Kreislaufstörungen bei den Herzneurosen *Ztschr f d ges. exper Med.*, 34 71 1923
- 11 Douglas Wilson, I Somatic Manifestations of Psychoneurosis *Brit. M J.*, March 25 1944
- 12 Dunbar Flanders Emotions and Bodily Changes New York Columbia University Press 1938 p 641
- 13 Dunbar Flanders Psychosomatic Diagnosis. New York Paul B Hoeber Inc., 1943 p 741
- 14 Dunn W H Emotional Factors in Neurocirculatory Asthenia *Psychosom Med.*, 4 333 (Oct.) 1942
- 15 Dunn W H Gastroduodenal Disorders, an Important Wartime Medical Problem. Josiah Macy Jr., Foundation 565 Park Ave., New York 1942
- 16 Editorial Dyspepsia in the Army *Brit M J.*, 2 836 (Dec. 14) 1940
- 17 Editorial Dyspepsia in the Army *Lancet*, 1946 (Jan 11) 1941
- 18 Editorial Peptic Ulcer—the Major Disability in Wartime *Canad M A J.*, 44 508 (May) 1941
- 19 Erickson, M H Hypnotic Suggestion of Psychosomatic Phenomena *Psychosomatic Interrelationships Studied by Experimental Hypnosis Psychosom Med* 5 51 (Jan) 1943
- 20 Fulton J F and Ingraham, F D *J Physiol.*, 67 27, 1929
- 21 Gagel, O The Hypothalamus Bumke Foerster *Handbuch der Neurologie.* Berlin Springer 5482, 1936
- 22 Grinker R. R. and Spiegel J P Brief Psychotherapy in War Neuroses. *Psychosom Med.*, 6 123 (April) 1944
- 23 Halliday J L Rising Incidence of Psychosomatic Illness. *Brit. M J.*, 2 11 (July 2) 1938
- 24 Heath R G and Powdermaker F Use of Ergotamine Tartrate as a Remedy for "Battle Reaction" *J.A.M.A.*, 125 111 (May 13) 1944
- 25 Hoch P H Psychopathology of Traumatic War Neuroses *Am J Psychiat.*, 100 124 (July) 1943

- 26 Kardiner, A Forensic Issues in the Neuroses of War *Am J Psychiat.*, 99 654 (March) 1943
- 27 Kasanin, J Defense Reactions in Anxiety States of Central Origin *Psychoanalyt Quart.*, 11 493, 1943
- 28 Masserman, J H Is the Hypothalamus a Center of Emotion? *Psychosom Med.*, 3 3 (Jan) 1941
- 29 Mittelman, B and Wolff, H G Emotions and Gastrointestinal Function, Experimental Studies on Patients with Gastritis, Duodenitis and Peptic Ulcer *Psychosom Med.*, 4 5 (Jan) 1942
- 30 Murray, J H Some Special Aspects of Psychotherapy in the Army Air Forces *Psychosom Med.*, 6 119 (April) 1944
- 31 Psychosomatic Medicine Journal established 1939 Williams & Wilkins Co., Baltimore
- 32 Raines, G N and Kolb, L Combat Fatigue and War Neurosis *US Nav M Bull.*, 41 923 (July) 1943, 41 1299 (Sept) 1943
- 33 Rosner, A A The Psychiatric Sequelae of Epidemic Encephalitis Chap VII, Encephalitis—a Clinical Study, Josephine B Neal and others For the Matheson Commission for Research in Epidemic Encephalitis New York, Grune and Stratton, 1942, p 563
- 34 Rosner, A A Unit Reaction States in Oculogyric Crises *Am J Psychiat.*, 99 224 (Sept) 1942
- 35 Rosner, A A Neuropsychiatric Casualties from Guadalcanal 1 Persistent Symptoms in Three Cases *Am J Med Sc.*, 209 770 (June) 1944
- 36 Rosner, A A The Neuropsychiatrist and Convalescent Training Program of Army Air Forces *Bull US Army M Dept.*, 78-93 (July) 1944
- 37 Rosner, A A A Mental Hygiene Unit in the Army Air Forces Accepted for Publication *Bull US Army M Dept*
- 38 Schwab, R S., Finesinger, J E and Brazier, M A B Psychoneurosis Precipitated by Combat *US Nav M Bull.*, 42 535 (March) 1944
- 39 Sheehan, D Some Physiological Principles Underlying Variability of Response *Ann New York Acad Sc.*, 44 551 (Dec 22) 1943
- 40 Silverman, J J and Powell, V E Studies in Palmar Sweating *Psychosom Med.*, 6 243 (July) 1944
- 41 Smith, E. R Neuroses Resulting from Combat *Am J Psychiat.*, 100-94 (July) 1943
- 42 Strecker, Edward A Mental Hygiene Nelson's Loose-Leaf Living Medicine, Vol VII, Chap XII
- 43 Symposium Abuse of Rest *JAMA*, 16 1075-1092 (Aug 19) 1944
- 44 Tidy, H Peptic Ulcer and Dyspepsia in the Army *Brit. M J.*, 2 473 (Oct 16) 1943
- 45 Torie, A and Aherd, M B Psychosomatic Casualties in the Middle East. *Lancet*, 1 139 (Jan 29) 1944
- 46 Weiss, Edward and English, O Spurgeon Psychosomatic Medicine Philadelphia, W B Saunders Co., 1943
- 47 Wolff, H G Disturbances of Gastrointestinal Function in Relation to Personality Disorders *Ann New York Acad Sc.*, 44 567 (Dec 22) 1943

# RECONDITIONING OF TRANSITORILY MALADJUSTED SOLDIERS

COLONEL THOMAS G. TOUSEY

MEDICAL CORPS, UNITED STATES ARMY

This article deals only with those soldiers who have had to be removed from task force units at a staging camp, while en route overseas, for a mental condition ordinarily recognized as psychoneurosis. A careful study of a large number of these cases leads to the conclusion that they mostly were soldiers temporarily out of harmony with their environments rather than afflicted with a true mental disorder of psychogenic origin. In other words, it was felt that they were maladjusted rather than psychoneurotic. Their symptoms on admission uniformly were severe enough to warrant their being removed from task force units but, because many of them were revealing symptoms for the first time, it was felt that these symptoms were temporary and were precipitated because of apprehension arising from thoughts of impending embarkation. It must be remembered that all of this personnel had been through months or years of training and maneuvers and should have been inured to all war conditions short of actual combat. It also must be kept in mind that because of the training they had undergone they were especially valuable to the Army and the war effort and their prompt reconditioning was most important. It was for these reasons that the 'maladjusted regimen,' as it was called, was established at a camp in March, 1943.

## PROBLEMS PRESENTED BY MALADJUSTED PERSONNEL

There were several possible approaches to the problems presented by this personnel. These men could have been subjected to a program similar to patient reconditioning programs now conducted in all Army hospitals, or they could have been transferred to special training battalions under command of line officers, or they could have been labeled psychoneurotic and considered to have lost all usefulness to the Army and have been discharged.

Early in 1943 it was realized that the number of soldiers being discharged from the Army with the diagnosis of psychoneurosis was very great. Newspaper and popular magazine articles on psychoneurosis were becoming more frequent and it was not uncommon to hear civilians jokingly remark about psychoneurotics getting out of the Army. Thoughtful civilians were taking a more serious view of the matter and were showing their concern for the Army because of the large numbers being let out with the diagnosis of psychoneurosis for the individuals themselves who, with the stigma of the diagnosis, were



finding it difficult to get employment, and because of the implication that the younger generation did not have the mental stamina commonly ascribed to youthful Americans. Because of these observations, follow-up letters were sent to the next of kin of all who had been discharged from the Army at this camp for psychoneurosis, and from the replies it was evident that the great majority had adjusted themselves to their civilian environment almost immediately after separation from the service. The questionnaires clearly indicated that freedom from military restraint, loss of cause for apprehension, and cessation of letters and messages from home that caused emotional storms, coupled with the privileges of continuous liberty and comforts of an agreeable environment, were the dominating reasons.

The composite psychoneurotic, therefore, as seen at this camp, is one without the mental stamina to undergo severe or unusual strain. He came into the Army that way and his mental conditioning was not completed during his training. This is partly because a line commander cannot evaluate evidences of lack of mental stability with the same ease that he can a lowered physical state. This fact emphasizes the need for a short, practical course for company officers in methods of detecting mental upsets.

To develop a system or plan for reconditioning these individuals to the degree that they once again would be useful members of the military establishment, it was necessary first to understand fully the composite psychoneurotic and how to determine his peculiarities. First of all, he is a tense individual with a stormy mind surrounded with a shell of resistance to outside influences from which he cannot escape without help. That bizarre definition forms the basis of the plan of treatment used successfully for one and a half years.

#### CAUSES AND SIGNS OF MALADJUSTMENT

Why should an individual withdraw into a shell? Just as a person quickly withdraws his hand when he touches something hot, so a soldier withdraws mentally from something that irritates his sensorium. He is irritated by restraints, the "musts" of army life. Varying and ever-increasing degrees of apprehension cause a subconscious withdrawal and soon he develops a resistance to circumstances that ordinarily would cause him no concern. To further aggravate the condition, he writes of his unpleasant situation to members of his family who with normal sympathy reply with letters that create emotional storms. The officer who commands the soldier inflicts punishments for derelictions, causing resentment and an inferiority complex, and the build-up for the diagnosis of psychoneurosis is complete.

From the clinical side, the maladjusted soldier presents certain general complaints, the most common of which are as follows: general weakness, 60 per cent, depression, headaches, general body pains, each 50 per cent, insomnia, 30 per cent, and loss of appetite, 26 per cent.

In the early stages of his training a soldier is credulous and tractable, and an incipient condition could and should be recognized. He should be helped then by proper orientation and suggestion. By the time he reaches a port of embarkation staging camp and is ready to sail to a theater of operations his shell has become so dense that treatment away from his unit is necessary. Each such case represents a loss of manpower in an Army that desperately needs every fighting man. More emphasis must be placed on early mental conditioning which would obviate the need for much reconditioning. During training periods it should be required that unit medical officers constantly accompany troops on every training exercise into the field and devote much of their time to making observations of personnel. Too much time is spent in dispensaries in base camps waiting for things to happen. Every time a soldier falls out of a formation or lags on marches, there is a physical or mental reason and he should be studied on the spot by the accompanying medical officer.

#### PRINCIPLES OF MANAGEMENT

The principles involved in the management of maladjusted personnel at a staging area included

- 1 The avoidance of the diagnosis of psychoneurosis until such time as it is fully determined that the soldier cannot be restored to useful military service and must be discharged. It was found that a soldier, if told that he is a psychoneurotic, will quickly add depression to the rest of his symptoms and will be that much harder to approach. It has been noted also that in their efforts to get themselves discharged from the service they feel that if they have psychoneurosis they are entitled to immediate separation and any attempts at reconditioning are resented and therefore impeded.

- 2 The second principle is to return all such personnel to full duty status as soon as their symptoms are recognized—approximately one week after admission—so that they may be assigned work of a useful nature. This is important, for these individuals become impatient with temporizing procedures such as the minor craft work often carried on in hospitals. They are men and in their reconditioning we must remember that we are dealing with men's minds.

- 3 Rest, in its true sense, also is important. It must be remembered however, that "absence of occupation is not rest, a mind quite vacant is a mind distressed." Healthful discussions and orientation talks serve to supply thoughts that will afford mental rest.

- 4 Again it is necessary to make a soldier realize the importance to himself of his own reconditioning. He must be inspired to readjust himself and to understand that in so doing he will gain self-confidence necessary to his complete restoration.

- 5 Dispersion of maladjusted individuals, as they are known in this program among normal troops is essential. It was discovered early that

when housed together, even on a duty status, some felt that the finger of mockery was pointed at them. They, therefore, are scattered among other troops for duty, rations and quarters. In fact, other troops are not cognizant that maladjusted soldiers are other than newly assigned or attached personnel. This dispersion also precludes several from getting together to discuss their symptoms. There is one in every such group who will dominate all and may exercise a bad influence.

6 It is important to make all in the group feel that they are normal soldiers living, working, playing and conducting themselves as would normal soldiers. This association with normal soldiers has served to stimulate, through pride, a desire to correct their own weaknesses. It also prevents unwarranted solicitous attention from others.

7 Lastly, duties assigned these individuals initially must be within their capabilities and of such a nature that quickly attained results in which they can take pride are certain. Nonfulfillment of purpose causes a bad reaction in the early processes of reconditioning. All soldiers are encouraged to work well, to think for themselves, and to absorb responsibilities incident to the task at hand.

#### MEANS OF GAINING THE INITIAL CONTACT

But before any of these principles can be applied it is necessary to penetrate the shells of resistance built up about their conscious selves. This initial entry into a mentally disturbed man's inner self is the most difficult part of the problem of his reconditioning and the most important part. Once such an entry has been made, it is found the soldier has developed sufficient confidence in those helping him so that he becomes amenable to progressive suggestions. This phase of treatment should be started while the soldier is still on a patient status.

It has been found that there are many ways of gaining this initial contact. Arousing his interest in something new to him has been the most successful. A skilled soldier artist develops the first contact with some by teaching soldier patients some of the basic principles of sketching and incidentally has them draw pictures. They are surprised at their ability and their interest is aroused. Some of the more difficult patients have been started through this means. Clay modeling has proved equally effective, partly because it is a creative art and its results are quickly apparent and usually are highly satisfactory. Those conducting such classes must not only be artists, they must be psychologists and sincerely interested in the therapy they are carrying out. Gardening in season stands high as a method of gaining access to a patient's confidence and, in addition, access gained through this means leads to more rapid progress of the patient toward recovery. Gardening affords fresh air and sunshine, general body exercise of varying degrees, stimulation of the mind by the mere process of watching things grow, the sense of useful production, and the satisfaction of personal gain by eating the fruits and vegetables. But those

items do not constitute the only benefits derived from gardening therapy. As a man works in the garden he "rests," his tension eases, his "guards are down" so to speak, and he is less resistant to helpful indoctrination. Those conducting this training are well versed in amateur gardening and, more important, they have a thorough knowledge of this purpose of the reconditioning program. Members of garden clubs are particularly valuable for this work, especially when the amateur gardener also is a trained nurse with deep, sympathetic and practical understanding.

There are a variety of ways and means available to gain contact with these patients, to pierce their shells. Other facilities available at this camp include a carpenter shop, furniture repair shop and printing shop. It will again be noted that only facilities in which practical and masculine work is done are utilized. The carpenter shop is used only for repair work of a general camp utility nature such as repairing screens, rehanging doors, making shelves and other "gadgets" needed about the hospital. Many patients of their own volition have devised useful articles for the wards and made them in the shop. The furniture repair section rebuilds broken or damaged furniture not only for the hospital but for the entire camp. Overstuffed chairs and sofas are torn down to the bare frame and brought back to full usefulness again. In the print shop type is set for letterheads and other forms and the printing accomplished. A small weekly hospital paper also is printed here.

In these various facilities it is nearly always found that one of the work projects will arouse a sufficient demonstration of interest to permit a patient to go on to duty therapy. Sometimes a judicious shifting of a patient from one facility to another is required to gain the desired early reaction, but shifting is carried out with caution as patients often resist or resent reconditioning processes initially and invite changes of work during the initial stages to delay the procedure.

#### FULL DUTY PERIOD OF RECONDITIONING

Following this initial breakthrough the soldier is quickly discharged from the hospital to a full duty status. Some patients are, in fact, ready for full duty with training units at this time. Most, however, are found to need medical supervision during the early days of their full duty period, and so, on request of the hospital commander to the post commander, the soldier is attached to the Medical Detachment for duty, rations and quarters. It is most important that the transfer from patient status to the full duty status be made as early as practical to prevent patients from developing a mental condition comparable to the physical condition known as "drug fastness." This reconditioning therapy fastness must be avoided at all costs as it is hard to overcome. Rapid progress must be attained up to the point at which the patient begins to proceed normally about his assigned duties.

In transferring patients from hospital status to full duty, the administrative procedures are simple. A notice is forwarded to the Post Commander stating that the patient will be discharged from the hospital to duty and requesting that he be attached to the Medical Detachment for duty, rations and quarters until such time as he is considered fit for return to his own or some other organization. This procedure, of course, had been approved at the institution of the program. The soldier is discharged by action of the Hospital Disposition Board and goes to the Replacement Pool, to which he was assigned when his unit departed for overseas, assembles his clothing and equipment, and then reports to the Medical Detachment Commander for duty.

The procedure is normal in all ways and so soldiers about the hospital have no knowledge that the new soldier has ever been a patient in the mental wards. He is assigned to a barrack, care being taken that maladjusted trainees are not grouped in any one platoon. To all intents and purposes, all personnel so assigned are simply soldiers attached for duty and there is no stigma connected with them in any way. The Detachment Commander is a carefully selected officer who understands men and who is respected by them under all conditions. He personally interviews all soldiers who are assigned or attached to his unit, including those attached for maladjusted training. After a carefully conducted interview, he assigns each to a definite duty in the medical service, and at one time or another, almost every position in the hospital has been filled by one or more maladjusted soldiers.

Immediately following assignment the soldier comes under the notice of three officers who will observe his actions and reactions, his attention to duty, and all other military qualifications that a good soldier should have while in the service. The observations are made without the soldier's knowledge and without consultation between the officers. Every ten days each officer makes a brief narrative report on each maladjusted soldier to the Hospital Commander, from which is judged the progress being made by each. One of the reporting officers, the Detachment Commander, is not a medical officer so his estimates are based on an appraisal such as any line commander would make and not on professional judgment. He reports on the soldier's neatness and military bearing, his attitude toward other soldiers, particularly non-commissioned officers, in the barracks, at mess, or at work, is he a good mixer or does he stay by himself? If he has any habits not compatible with good military discipline, it is made a matter of record. Is he prompt at formations, does he complain about his status or his environment? What is his attitude toward the Army, the country, the war? This information all must be gained by observation, not questioning, for this soldier is on a duty status and he must not be made, to any degree, to feel he is a patient or that his every action is being watched.

EXAMPLE 1 (Report by Detachment Commanding Officer) " ————— is a conscientious worker, shows some initiative, tries to keep himself busy. He seems to be rather happy in his job. He is neat and courteous and has made no complaints of any physical ailments. He is trying and wants to learn the routine in the dispensary."

Another officer to report regularly on each maladjusted soldier is the officer under whom he works. This officer may or may not be a medical officer and the report is made from a viewpoint other than professional. How does the soldier apply himself to his work? Does he carry out his duties without urging? Is his interest aroused or sustained? Does he cooperate with others? Accuracy, speed, and demeanor are other subjects of this report. Progress made in essential elements since entering the maladjusted group is particularly important as an item of report.

EXAMPLE 2 (Report by officer under whom soldier is working) " ————— is excellent. I would like to have more like him. He has learned to give shots and to handle the sick book. With a little more training he could almost be called a full fledged dispensary man. I doubt if he could ever do heavy work because he gets badly 'winded'. At the moment he is upset because he is classed as maladjusted. He says he is working hard to overcome his nervous upset and he is doing a grand job."

The third officer who regularly reports on the progress of the maladjusted personnel is the psychiatrist. His approach to each individual is that of the doctor recently in charge of the case and who is, therefore, interested in his progress. By informal talks in the corridors, at the place of the soldier's duty, or at times, in the office of the psychiatrist, he determines from his professional viewpoint the mental state of the soldier and whether the soldier is progressively improving. He offers in his report such recommendations as may be indicated.

EXAMPLE 3 (Report by psychiatrist) "This soldier was making a satisfactory adjustment as long as he was in the dispensary. He has recently been assigned to the carpenter shop where the noise affected him badly. He is now more tense and anxious. It is recommended that he be reassigned to dispensary work."

(Note: The limitations on this soldier's readjustment noted over a period of four weeks led to his assignment to the Station Hospital Detachment, where during the past several months he has carried out his duties in a dispensary in a superior manner and he released a general military service soldier for overseas duty.)

From the assembled reports the Hospital Commander judges the status of each individual and directs his future handling. When a soldier makes highly satisfactory progress, his trial in a department where the work is of an entirely different nature is directed. Every effort is made to detect limitations on readjustment and also to determine just how best the readjusted soldier's services can be utilized. All soldiers

are pressed to accept more and more responsibilities in their work. A noncommissioned officer, before final recommendations for his disposition are made, is put in charge of some detail to determine how far he can be trusted to handle other men. Finally one of the following recommendations is sent to his unit commander who, in practically all cases in a staging camp, is the commanding officer of the Replacement Pool.

1 This soldier is returned to full military duty.

2 This soldier is returned to duty with the recommendation that his military service be limited to the United States. He has shown special adaptability as a (cook).

3 This soldier is returned to duty. Because of his tendency to (persistent dizziness) it is recommended that he be assigned to the Station Complement Medical Detachment, or to a similar unit in another camp, where he will be under close supervision of medical officers. He has shown special adaptability as a (clerk).

4 This soldier has not reacted well during his duty in the Maladjusted Regiment, is not considered suitable for retention in the Army, and will be discharged on Certificate of Disability, diagnosis, psychoneurosis.

During the latter stages of their readjustment, this personnel reports to an assembly point one hour each day, where orientation talks are given. One day each week a somewhat detailed account of war activities is given them and they are shown war or training films. On all other days talks are given by business and professional men from the nearby communities who volunteered their services. These are sound, practical and stimulating talks designed to broaden interests. They are excellently received.

#### SUMMARY AND CONCLUSIONS

To restate briefly, the treatment utilized in the Maladjusted Regiment consists of two phases, i.e., the breakdown of the soldier's resistance to reconditioning through stimulation of interest in one of the shops or in the garden, during a very brief period, and the full duty period with one hour a day orientation. Throughout the training, special care is given to the physical build-up through calisthenic exercise, marches and other activities taken with the Medical Detachment. Special facilities also are furnished so that all can take sun baths daily under the careful control of technicians.

In conclusion, it is desirable to emphasize the simplicity of the program for maladjusted soldiers through work therapy. It strengthens the mental fabric of an individual to the degree that his mental armor is able to resist impacts from whatever source. He gains confidence and pride in himself to the extent that he overcomes obsessions, inhibitions and neurasthenic blocks. He is less credulous. Through his continuous performance of useful military duties and his mingling with highly trained troops he develops new interests in military matters. The pe-

mod of duty therapy also offers the psychiatrist an excellent opportunity to study and evaluate various symptoms and arrive at a sound decision

The early removing of maladjusted personnel from the ward atmosphere is believed to be one of the most important principles of treatment because it immediately frees his mind of a real care. The work performed by the individual incident to his duty assignment is the factor that braces him against recurrences



# RECONDITIONING THE MALARIA PATIENT

CAPTAIN WILLIAM L. NOE, JR. AND MAJOR EARL W. PARKS  
MEDICAL CORPS, ARMY OF UNITED STATES

ALTHOUGH therapy of the acute attack of malaria with atabrine or quinine is highly effective, no known form of treatment will *prevent chronic relapses* in a certain percentage (perhaps 10 per cent) of all individuals who are infected. Some patients who have been observed have had relapses a dozen times at approximately monthly intervals, and still others have undergone twenty or more relapses. The management of the semi-invalidism associated with this chronic relapsing type of malaria is essentially a military problem at present, but is likely to become an important consideration in civilian medical practice following demobilization of the armed forces.

Inasmuch as relapsing malaria not only lowers the physical stamina of the patient, but also lowers his morale, it is now well recognized that the soldier with this disease requires, in addition to drug therapy, other forms of treatment. In order to accomplish this purpose, a Reconditioning Program has been developed at Hammond General Hospital which has proved highly satisfactory in a number of respects.<sup>1</sup> The program has been divided into two sections. The first includes only the hospitalized patients and is carried out on the wards of the Tropical Disease Section of the Medical Service. The second is carried out at the Advanced Reconditioning Center apart from the hospital where the patients live in army barracks. The reconditioning program in each of these two sections will be discussed separately. The institution of this program was facilitated by the Comprehensive War Department Reconditioning Program under the direction of which all patients in military hospitals, except those who are seriously ill or those in whom any slight exercise might have a deleterious effect, are required to undergo graduated series of exercises.<sup>2</sup> Depending upon their physical tolerance, the patients are classified into four groups. Briefly, Class IV includes bed patients who receive only slight exercise, perhaps limited to certain muscle groups or to certain parts of the body depending upon the disability that is present. Those in the remaining classes (III, II and I) receive graduated increasing physical activities so that those in Class I are able to perform physically in the manner that is required of a soldier on field duty. In addition, under the provisions of the War Department Reconditioning Program, all patients are encouraged to engage in vocational, diversional and educational activities.

## THE RECONDITIONING PROGRAM IN THE HOSPITAL

The hospital reconditioning program is concerned chiefly with adjusting the patient's morale to his relapsing illness, keeping him profitably occupied while he is in the hospital and preparing him physically for the Advanced Reconditioning Section. Only Class IV and III patients are cared for in the hospital, whereas Class II and I patients are observed at the Advanced Reconditioning Center away from the hospital atmosphere. Patients with acute malarial activity are confined to bed and do not participate in the Reconditioning Program. Under the optimum conditions that exist in a military hospital in the Continental United States, the general condition of patients after an acute attack of malarial fever is good so that the scope of their reconditioning activities can be increased quite rapidly following termination of the acute attack. Accordingly, they are started in Class IV as soon as the temperature has been normal for forty-eight hours, but must remain on the screened malarial wards until two successive blood smears taken forty-eight hours apart have been reported negative for parasites.

In order to aid their morale when these patients enter Class IV in the reconditioning program it is essential that the medical officers in charge reassure them that their chronic relapsing disease will eventually be cured without untoward and permanent sequelae. They are then urged to matriculate in any of the United States Armed Force Institute courses that they might choose. Occupational therapy in diverse forms is made available on the wards daily, a definite effort being put forth to guide this therapy in a vocational direction whenever possible. Books representing a wide range of educational and vocational subjects as well as recent "best sellers" are brought to the ward daily from the mobile branch of the Red Cross Library. The patients are encouraged to read on sociologic, economic, military and other problems relative to both the war and to the postwar reconstruction period.

Diversional therapy is also provided by the Red Cross and by other volunteer organizations. This diversional therapy consists partly in the presentation on the wards of sound motion pictures, shows and entertainments by United Service Organization Troupes, and partly in games such as ping-pong, croquet and shuffle board, which are available either on the ward or in the immediate environment (for Class III patients). The patients in Class IV also take part in mild calisthenics either in the ward or in a special screened enclosure adjacent to the ward. It should be pointed out here that this extensive program is made possible only through the close cooperation of the medical service with other agencies in the hospital such as the Red Cross, the reconditioning branch, the orientation and educational officer, the special service officer, and the occupational therapy division. These features of the program are extended throughout the period that the patient is in the advanced reconditioning center and until he is returned to duty.

Within one week of an acute attack, patients have usually recovered sufficiently to be advanced from Class IV to Class III. They are then able to leave the screened malarial wards so that they can attend lectures embracing a variety of timely subjects, which are given either by other hospital patients who have returned from overseas theaters of operations, by the orientation officer or his assistants, or by members of the faculty of nearby colleges. The patients may now also be granted passes which permit them to leave the hospital grounds for short periods. By this time the type of duty that is best suited to the individual patient has been selected by the Reclassification Officer after consideration of the patient's skills, army experience and physical condition.

A special effort is made during this period to recondition the patient to the amount of physical activity which will approach that expected of him when he is returned to duty status. Calisthenics are given out-of-doors, adjacent to the ward, at a regular time each day under the supervision of a physical education instructor. These exercises, together with competitive games such as volley ball, shooting baskets, tossing a baseball or football, are gradually increased in duration and intensity as they are tolerated. If the patient is able to gain weight or to maintain his normal weight, and to possess a general sense of well being, and if he is free of malarial activity for approximately two weeks while indulging in fairly vigorous and prolonged exercise, he is transferred from the hospital to Class II at the Advanced Reconditioning Center for further training.

#### THE RECONDITIONING PROGRAM AT THE ADVANCED RECONDITIONING CENTER

The chief mission of the Advanced Reconditioning Center, as stated by Brigadier General John M. Willis,<sup>3</sup> is to return the soldier to duty in the best possible condition in the shortest possible time. During the course of study of patients with malaria and other conditions at the advanced center of this hospital, a number of observations have been made with regard to best accomplishing this aim. The patient with malaria presents many special problems in reconditioning. One of these is the fact that, in addition to malaria, he may also suffer from a battle wound or have some other disease. Another is that, according to some authorities, exercise may increase the probability of, or induce a recurrence of, an acute attack of malaria. The reconditioning program has afforded an excellent opportunity to study this latter aspect of the problem, inasmuch as these patients, who are designated as trainees, undergo a progressive physical training program, including modified and remedial calisthenics, military drill, sports, hikes and work details.

The basis for this report of the Advanced Center is the observation of sixty-four patients with malaria who were observed during the

three months' period from June to August, 1944. These patients were transferred from the Medical Service after they were considered to have reached maximum hospital improvement, were ambulatory and had taken part in calisthenics of the Class III group. They were physically capable of participating in Class II of the Reconditioning Program. These patients had been evacuated from endemic malarial areas of the Southwest Pacific and North Africa, two to thirteen months previously. In all of these patients the diagnosis of malaria was conclusively established. Eighteen of the group were considered by the Medical Service to have chronic relapsing malaria, since each of them had exhibited five or more recurrences of malaria over an average period of five months.

When they reached the Advanced Reconditioning Center each one of the group of sixty-four patients was classified as a Class II trainee. It was planned to retain these patients in Class II for approximately two weeks, and then to transfer those who appeared to possess the necessary physical stamina to Class I. However, none of them were ever qualified for Class I as this advancement required the patients to demonstrate their fitness by executing satisfactorily a series of specified physical efficiency tests and completing a 15-mile hike. Consequently those who were sent to duty were discharged directly from Class II with certain specified physical limitations.

Analysis of this entire group of sixty-four patients reveals that thirty-seven patients or 57.7 per cent developed a malarial relapse after an average period of 36.7 days at the Advanced Reconditioning Center. Eight patients of the group had two relapses, an average of 31.2 days intervening between the first and second recurrences in each of these. These figures are of particular interest when they are compared with a series of 216 similar patients with malaria observed under hospital conditions over a period of thirteen consecutive weeks before the institution of the reconditioning program. These hospital patients regardless of the type of malarial drug treatment they received showed a relapse rate of 57 per cent with an average of thirty-four days intervening between relapses.

#### COMMENT

At present, available statistics are not conclusive regarding the probable termination of the course of relapsing *Plasmodium vivax* infection or the establishment of an average period which may elapse between the first recurrence date and final cure in patients evacuated from endemic malarial areas of the Southwest Pacific and North Africa. Studies of data compiled at Hammond General Hospital indicate that longer periods of observation are necessary in order to clarify this perplexing problem, particularly in view of the fact that the relapse rate of malaria patients may vary markedly. More definite information will undoubtedly be available in the near future.

In this series of cases the relapse rate of malaria patients with *P. vivax* type of infection who were observed at the Advanced Reconditioning Section was the same as that of the control series of 216 similar cases managed entirely under restricted hospital conditions. In view of these findings the advantage of placing this type of malaria patient in an Advanced Physical Reconditioning Program might be questioned. However, it is generally recognized that patients who remain in the hospital for prolonged periods of time are apt to become introspective, develop fixation of their symptoms and manifest varying degrees of psychoneurotic symptoms. This is one of the major points which the War Department Reconditioning Program seeks to correct. For this reason and inasmuch as the relapse rate was identical in the two groups, and since there was demonstrated an improvement in mental attitude and desire to return to duty in those patients who underwent physical exercise at the Advanced Reconditioning Center, it is felt that these patients should be transferred to this section as soon as possible rather than undergo continuous observation of a hospital regimen type in a hospital atmosphere.

#### SUMMARY

1 The problems involved and the methods utilized in carrying out the War Department reconditioning program in patients with chronic relapsing malaria in a military general hospital in the zone of the interior are cited.

2 An attempt has been made to observe the effect of physical exercise upon the relapse rate of recurrent *Plasmodium vivax* malarial fever.

3 Sixty-four patients with chronic recurring malaria were observed in the Advanced Reconditioning Center of a military general hospital for a period of three months. The average relapse rate was 57.7 per cent and the average period between relapses was 36.7 days.

4 A control series of 216 similar patients were observed under hospital conditions over a period of thirteen weeks. The average relapse rate was 57 per cent and the average period between relapses was thirty-four days.

5 From a military standpoint, the care of these patients in an Advanced Reconditioning Center away from the hospital atmosphere appears advisable.

#### BIBLIOGRAPHY

- 1 Ninth Service Command Reconditioning Conference, Hammond General Hospital, Modesto, California, June 17, 1944, p. 71.
- 2 Memorandum Number W40-6-43 February 11, 1943 "Convalescence and Reconditioning in Hospitals," Surgeon General's Office Circular Letter Number 168, September 21, 1943.
- 3 Ninth Service Command Reconditioning Conference, Hammond General Hospital, Modesto, California, June 16, 1944, p. 49.

## THE CONVALESCENT CARE OF RHEUMATIC FEVER IN THE ARMY AIR FORCES

LT COLONEL IRVING ERSHLER

MEDICAL CORPS ARMY OF THE UNITED STATES

THE occurrence in 1942 and 1943 of a large number of cases of acute rheumatic fever among personnel of the Army Air Forces was the stimulus for the development in the spring of 1943 of a Rheumatic Fever Control Program. The details of the overall program have been described elsewhere.<sup>1</sup> Forty of the larger AAF hospitals were selected to cooperate in the program. The posts chosen for study were in areas of high incidence of rheumatic fever, in areas of low incidence, and in intermediate areas. Laboratories have been set up with the equipment and personnel needed for grouping and typing of hemolytic streptococci. Rheumatic fever was made a reportable disease on the weekly statistical report and a central registry of all cases of rheumatic fever is maintained in the Office of the Air Surgeon. As one phase of the rheumatic fever control study, a definitive convalescent program was developed.

Ideal care of patients with rheumatic fever involves adequate medical care during the acute and subacute phases of the disease, provision for long term medical follow-up, hospitalization and nursing care during the acute phase of the illness, prolonged hospitalization and nursing care for the occasional patient with chronic progressive disease, arrangement for protracted bed care in sanatoria, convalescent homes or in the patient's home following discharge from the hospital, medical-social service facilities to make available welfare resources where needed and to assist in follow-up studies, provision for schooling, occupational therapy, and in some cases vocational training, and residence in an area of low incidence of rheumatic fever for a prolonged period of time following recovery to minimize the possibility of recurrence.

The complexity of adequate care and the low economic level of many patients make the proper treatment of rheumatic fever expensive and too time-consuming for the physician. For these reasons it has not been possible to supply adequate care for any large group of rheumatic fever patients in this country. In the AAF Rheumatic Fever Control Program, an attempt has been made to supply as close to ideal care as possible for these patients. The convalescent aspect of the program has three major phases: medical, physical training, and vocational

---

From the Army Air Forces Rheumatic Fever Control Program.

## MEDICAL PHASE

In general, the usually accepted conservative precepts in regard to the management of rheumatic fever are adhered to. Of particular interest is an attempted standardization of criteria for diagnosis following Jones.<sup>2</sup> The necessity for uniform criteria has been appreciated by all workers. Variations in some details of management, particularly treatment, occur due to individual medical viewpoints.

The usual case of rheumatic fever is hospitalized at the AAF Station Hospital on the post where the illness occurs or at the nearest AAF Regional Hospital. As soon as the patient can be transported safely he is moved to one of a group of AAF Regional Hospitals designated for the convalescent care of rheumatic fever. The hospitals in this group are all below the 34th parallel in the United States and are in areas of low incidence of rheumatic fever. The latter has been ascertained both by clinical experience and by a comprehensive bacteriological survey of the distribution of Group A hemolytic streptococci and its relationship to the incidence of rheumatic fever.<sup>3</sup> Rheumatic fever patients are kept at the hospitals designated for convalescent care for a period of six months after the onset of the illness or for any extension of this period necessary for maximal recovery. The only exception to this rule is in the case of those patients who are to be separated from the service because of unusually severe rheumatic fever or its sequelae. These patients are discharged from the Army on the completion of maximum hospital benefits. Personnel are separated from the service because of rheumatic fever if the active phase of the disease has been unduly long, if there is persistent heart failure or cardiac enlargement following the acute phase of the disease, if there has been a previous attack within two years or if there is residual cardiac disease at the end of the period of hospitalization. Exception to the last provision may be made in the case of highly skilled personnel who may be utilized on a restricted activity basis if the residual cardiac disease has static characteristics and is without evidence of significant impairment of cardiac function. To date, approximately 70 per cent of all patients with rheumatic fever are returning to duty.

Upon completion of treatment at the hospitals designated for convalescent care, personnel are assigned for duty for an additional six months' period to AAF Stations in the continental United States in areas of low incidence of rheumatic fever. In general, areas of the United States south of the 34th parallel (below the 36th parallel in California) can be considered to be areas of low incidence of rheumatic fever and are recommended for assignment. Upon termination of six months' duty in such an assignment, these individuals are reexamined and, if found to be free from evidence of rheumatic fever or its sequelae, and otherwise physically qualified, are declared fit for general duty. The only exceptions to this are the skilled personnel with residual cardiac disease noted above. If these individuals are retained

in service they are assigned to duty in an area of low incidence and disqualified for transfer overseas.

Under this plan patients with rheumatic fever are under expert medical observation for a minimal period of six months, following this, medical care is readily available as long as they remain in the Army. Medical follow-up is possible during this time and arrangements are now being made for a long term study of these individuals following separation from the service. Hospitalization and nursing care are available during the acute and convalescent phases of the illness. The transfer to hospitals in areas of low incidence of rheumatic fever for convalescent care and the subsequent assignment of these individuals to duty for six months at stations in similar areas of low incidence, provide the possibility of residence in low incidence areas for approximately ten to twelve months after the onset of the acute illness.

A frequent problem that occurs during the handling of patients with rheumatic fever is the development of anxiety states with resultant psychosomatic manifestations in many cases, as a result of the patient's knowledge of the serious heart complications of rheumatic fever and the necessity for frequent cardiac examinations, electrocardiograms, and so forth. In the convalescent program this problem has been minimized or obviated by the following measures: (1) appreciation of the problem by the responsible medical officers, (2) proper handling of each patient so as to insure the development of confidence in the physician, (3) a definite plan of explanation and reassurance to the patient, designed to correct erroneous ideas in relation to prognosis of the disease and, particularly, to point out the likelihood of complete functional recovery. This has taken the form of lectures, group psychotherapy, individual conferences, and/or psychiatric consultations where necessary, (4) avoidance of unnecessary examinations and the discussion in the presence of the patient of such findings as cardiac murmurs, prolonged P-R intervals and cardiac enlargement. Where the patient is in possession of such information, explanation and reassurance have proved to be particularly valuable, (5) a physical training program arranged so as to demonstrate to the patient that prior to returning to duty he is able to carry out vigorous exertion without difficulty.

Patients with established valvular defects who are returned to duty receive special consideration in regard to physical training. The tendency to anxiety in relation to the heart condition can be effectively allayed by encouragement to participate in as much physical activity as the individual's cardiac reserve permits. Many individuals with valvular lesions have no manifest loss of cardiac reserve and are capable of as much physical exertion as any normal person. A convalescent patient with a valvular defect who is to be returned to duty participates in the physical training program to the extent that his



permits in the judgment of the responsible medical officer. A rough guide to such an individual's ability to stand vigorous exercise is his demonstrated ability to participate without the development of chest pain, undue dyspnea or fatigue.

The prolonged hospitalization and medical observation necessary for the proper care of rheumatic fever has a tendency in itself to induce anxiety. To avoid this, as soon as the convalescents become fully ambulatory, they are moved from the hospital and housed in barracks under living conditions which approximate normal army life as closely as possible. They are required to adhere to a daily schedule that affords them the same liberties and disciplinary restrictions encountered in normal army duty. Except for periodic medical check-up they are thus removed entirely from a hospital atmosphere. In addition to its effect upon morale this housing plan provides a convenient arrangement from which the details of the physical training and vocational phases of the convalescent program, to be described below, are carried out.

Rheumatic fever has been considered a childhood disease. Information relative to pathogenesis and prognosis of at least the acute phase of this disease has been derived largely from the study of children. The occurrence of acute rheumatic fever in epidemic form in the armed forces, in many cases initial attacks, has focused attention upon acute rheumatic fever as an adult disease. In addition to routine medical care, certain studies are being done regarding the necessity for prolonged inactivity following acute rheumatic fever, the relationship between activity and recurrences, the relationship between early activation and the subsequent development of valvular defects, and the management of persistent streptococcus carriers in patients convalescing from rheumatic fever.

#### PHYSICAL TRAINING PHASE

The prolonged restriction of activity in the usual case of rheumatic fever necessitated an intensive, graduated program of physical training to insure that each convalescent returned to duty in the highest degree of physical fitness. This is one of the most important aspects of the convalescent program.

After joint symptoms and fever have subsided, if the general condition permits, physical training, in some cases, is started while the patient is still in bed. Mild passive and active bed exercises are used. Where joints have been involved for a long time, special muscle-setting exercises have been helpful.

Physiotherapists and specially qualified physical training personnel are available for this work. Some medical officers prefer to withhold all exercise until the erythrocyte sedimentation rate has returned to normal and the patient gotten out of bed. In all cases, when the patient is ambulatory, mild graduated calisthenics are started on the ward.

These are combined with less strenuous games, such as darts, croquet and shuffle board, as additional exercise is desired.

In the barracks phase of the convalescent program half of the day is devoted to a schedule of carefully supervised, graduated physical training. Calisthenics, close order drill, group games and hikes are the components of the program. The intensity of the various activities is gradually increased so that, prior to returning to duty, the convalescent is exercising on a level comparable to full duty activity. In addition to insuring maximum physical fitness upon return to duty, this program is of value psychologically as an indication to the patient of the extent of his functional recovery from rheumatic fever.

A standardized graduated physical training program is being used for both hospital ward and barracks phases of the convalescent program. Integrated with this program is a group of graduated physical fitness tests which are used, in conjunction with clinical observation, to determine the rate at which the convalescent is allowed to progress to the successively higher levels of physical activity.

This plan provides adequate physical retraining prior to the return of the convalescent patient to duty and ensures that each patient returns to duty in physical condition adequate for the performance of duty in his particular military occupational specialty.

#### VOCATIONAL PHASE

Rheumatic fever is usually incurred in the first year of an individual's Army experience. For this reason many patients with rheumatic fever have not completed training for a military occupational specialty. Personnel with certain military occupational specialties require reclassification because of rheumatic fever. Both of these groups of individuals, during the ambulatory phase of the convalescent program, are given schooling and/or on-the-job training so that, prior to returning to duty they are classified in an appropriate military occupational specialty. In this way the time available in the convalescent program is used as productively as possible, both for the service and for the individual.

Under this plan vocational training is available to all patients in the convalescent program. In addition to its psychological value in providing occupational therapy for the convalescent patient it offers the opportunity for any specialized training necessitated by possible physical limitations due to the sequelae of rheumatic fever.

#### CONCLUSIONS

A definitive convalescent program for patients with rheumatic fever has been developed by the Army Air Forces.

The program provides for adequate medical care and follow-up hospitalization and nursing care, convalescent care, physical retraining, schooling, occupational therapy, vocational training, and residence in

an area of low incidence of rheumatic fever for a period of ten twelve months after the onset of the acute illness

## BIBLIOGRAPHY

- 1 Holbrook, W Paul The Army Air Forces Rheumatic Fever Control Program J.A.M.A., 126 84 (Sept. 9) 1944
- 2 Jones, T D The Diagnosis of Rheumatic Fever J.A.M.A., 126 481 (Oct 2 1944
- 3 Van Ravenswaay, Arie C The Geographic Distribution of Hemolytic Streptococci Relationship to the Incidence of Rheumatic Fever J.A.M.A., 126 486 (Oct 21) 1944

# FATIGUE AND EXHAUSTION STATES IN THE ARMY AND IN INDUSTRY

JOSEPH L. FETTERMAN, M.D.\*

MAJOR, MEDICAL CORPS, UNITED STATES ARMY (RET)

FATIGUE and exhaustion cover a wide field whose boundaries extend from normal tiredness on exertion to acute nervous disorders. Ordinary fatigue is too well known or rather felt to deserve discussion here. We will, however, mention briefly the fatigue reactions occurring in industrial life, then discuss in greater length the more profound exhaustion states such as occur in military life. What causes them, how are they related to neuroses, how can they be prevented or treated?

## INDUSTRIAL FATIGUE

Industrial fatigue arises from a single cause or combination of factors such as prolonged hours of work, uncomfortable situations of temperature, humidity, dust, and unfavorable mental reactions. Prolonged exertion is of itself the most common cause of tiredness to the point of decreased output. Sayers<sup>1</sup> cites the experience of British munitions workers who, under the pressure of terrific need, worked seventy-four hours per week. When the working week was later reduced to fifty-five hours, the weekly output did not fall off, rather it was increased by 13 per cent. In some instances production was 10 per cent greater during a month when workers were made to stop work for four ten minute periods during a work day. Within limitations, a reduction in hours of work leads to an increase in hourly output so that the daily output rises (Sayers). Indeed, the fatigue factor of long hours without a rest day and without vacation so reduced productivity that Churchill announced, "If we are to win the war it will be largely by staying powers. For that purpose there must be one day in seven for a rest and as a general rule there must be one week's holiday a year."

But prolonged hours alone do not tell the whole story. The atmosphere both physical and social, is significant. The employee-employer relationship, provisions for safety, adequate rewards, incentives, all determine capacity and output. Again we may quote from Savers "Industrial fatigue is related to environmental conditions and relations with management and fellow workers. These are more important than

From the School of Medicine, Western Reserve University, Cleveland, Ohio.  
\* Formerly Executive Officer, School of Military Neuropsychiatry, Assistant Clinical Professor of Nervous and Mental Diseases, Western Reserve University (on leave of absence), Assistant Visiting Neurologist, University Hospitals.

physical activity except in the 'heavy' industries that require hard physical labor"

The workmen who dislike the kind of work they are doing, who are in a state of fear and tension because of its hazards, those who accumulate a growing resentment against their employers, such men and women readily become fatigued. Pent-up resentment and unexpressed hostility consume energy, lessen the benefit of rest, lead to earlier exhaustion.

Long hours of work leading to fatigue does not produce ill health. Sayers summarizes an extensive study of the literature on fatigue thus: "Data on fatigue and health show the connection between fatigue and loss of working efficiency and increased accident occurrence but there is little actual proof that long fatiguing periods of work permanently affect efficiency, health, or working capacity." We may interpret Sayers' conclusion to mean that continuous effort may lead to fatigue symptoms. However, these are reversible and the fatigue does not permanently affect health.

#### CAUSES OF FATIGUE AMONG FIGHTING FORCES

The factors that lead to fatigue in war are more numerous, more prolonged, and far more severe than in industry. Among working men it is one or a combination of prolonged hours, unfavorable environment, and psychologic factors. These same factors, far more disturbing, are present in warfare—and many more besides. The soldier must endure prolonged exertion, is exposed to weakening climate, suffers deprivations of food, of rest, of sleep, lives in a state of uncertainty, frustration, or actual fear. Periods of monotony or of tense worried anticipation are followed by ceaseless noise, long marching, and fighting in which buddies are being killed and his own life is in danger. Thus, the causes of fatigue are usually not single but multiple and their effect, cumulative.

**Exertion**—Fighting is tough. The soldier must take territory on foot—march in on the enemy. In attack as in retreat he has to hike along, uphill and across stream, in rain and snow and mud, weighed down by a heavy pack. He begins training with a hike of 5 miles, then he hikes 10 miles, then up to 25 and finally 30 miles with a full pack weighing over 50 pounds. During training he may enjoy the refreshing luxury of a rest and even have long sleep afterwards. Not so in combat. Then one day's march may be followed by another march with little or no rest. Picture the plight of the British Expeditionary Force retreating towards Dunkirk. Such a retreat means incessant plodding under bombing to reach the goal of safety. On other occasions soldiers may remain in the trenches for days of continuous firing with little or no rest. Here is a description from Hurst<sup>2</sup>: "Men who fought six days and nights—they were tired almost to death, and when called on to make one last effort after six days and nights of fighting and marching

many of them staggered like men who had been chloroformed, with dazed eyes, and grey and drawn faces speechless, deaf to words spoken to them, blind to menace about them, seemingly at the last gasp of strength. They had a drunken craving for sleep and slept standing with their heads falling against the parapet." Again let us follow the American foot soldier described so feelingly by Ernie Pyle<sup>3</sup> "Their nights have been violent with attack, fright, butchery, and their days sleepless and miserable with the crash of artillery. They are walking 50 feet apart for dispersal. Their walk is slow for they are weary every line and sag of their bodies speaks for their inhuman exhaustion. On their shoulders they carry heavy steel tripods, machine gun barrels, leaden boxes of ammunition. Their feet seem to sink into the ground from the overload they are bearing. They don't slouch. It is the terrible deliberation of each step that spells out their appalling tiredness. Their faces are black and unshaven. They are young men but the grime and whiskers and exhaustion makes them look middle aged."

Outfits who have landed on beaches, as in the Sicilian invasion, keep going for several days and nights without rest or sleep and then perhaps snatch an hour or two hours' rest as they go on and on. It may be two weeks before a soldier can relax for a refreshing night's sleep.

**Climatic Factors**—The hardship of soldiering is not alone the expenditure of muscular energy, it means also endurance of unfavorable climate. Picture the soldier from the south who made an amphibious landing in Attu in the Arctic, through cold waters, marching against a misty cold wind, and sleeping on freezing ground. Think of the many Americans, some from Maine and Michigan, who are stationed in the tropics, in Panama, in North Africa, in the islands of the South Pacific, the deserts of Iran, or tropical India. Such a soldier must endure the sands of the desert or the sweaty steam of the jungle at temperatures of 110° to 120° F, or even 140° F. An officer of engineers who helped construct a road through Iran for the shipping of supplies to Russia insists that he saw the thermometer reach 185° F in the sun at noon. He considered 120° to 140° F as common. It is no wonder many of our soldiers lose 20 to 30 pounds when they are in the tropics.

**Deficiencies** (In a general sense)—The human body to be comfortable and efficient needs rest and materials for replenishment. Deprived of rest, lacking sufficient chemicals, wanting adequate vitamins and calories, a person becomes uncomfortable, loses the capacity for first grade performance, and may develop sickness—if the defect is not corrected.

Despite the excellent precautions of our War Department, soldiers cannot escape deficiencies. First is lack of sleep. In warfare a soldier does not choose his bed and then sleep in it. His abode may be the ground, a foxhole, amidst heat and smell. Booming artillery jars him

Enemy planes return night after night, and the warning siren means a hurried run in darkness from the bed or sleeping bag into the fox-hole. Or the bitter cold of Iceland finally penetrates through the warm sleeping boots to awaken him, while he who is in the jungle cannot fall asleep because of the heat or insects.

Though our soldiers are among the best fed troops in the world, there are periods of unavoidable dietary deficiency. The men fighting in the desert lose chlorides from sweating and may go without sufficient water. Those in the front lines may be limited to canned rations and at times an insufficient number of them. One captain told of being several weeks in the front lines of Guadalcanal with a minimal amount of water so that he and his men drank from any pool or stream and subsisted upon one can of food daily. (The prescribed number was three or more cans in twenty-four hours.) He lost 30 pounds in six weeks. A corporal who was also in Guadalcanal, during his weeks in the front lines slept poorly, ate little, and also had diarrhea. When he reached the station hospital in a weak and nervous state his scaly skin and shiny tongue gave evidence of avitaminosis.

Thus the soldier is exposed to deficiencies of rest, of food, and may likewise be weakened by disease (infections from insect bites, diarrheas, malaria, and so forth).

**Psychologic Factors**—Coupled with the physical hardships of warfare is a succession of situations disturbing to the psyche. From the beginning of his training the soldier may be irked by the restrictions and regulations, troubled by unsolved and recurring problems at home, distressed by frustrations, emotionally disturbed by the preparations for combat. Some soldiers, previously timid, peace-loving civilians, may find it most trying to learn to shoot, are sensitive to the noise of artillery. Yet most of our men pass through this period of basic training and of maneuvers successfully. But the scene changes when the soldier has been transported to the zone of combat and has landed on enemy soil. In combat he is exposed to horrors and hardships that try men's souls (Paine). He is subjected to incessant noise, the sharp sound of rifle bullets, the boom of artillery, the shrieking siren of dive bombers. He must sit in the foxhole or march forward in the face of noise which spells death. He sees wounded and bleeding buddies, he witnesses death of friends and foe. Ahead of him behind a clump of trees is a sniper, or in the house on the hilltop is a deadly 88 mm gun spouting shells which explode dangerously near.

Confronted with these hazards every man is afraid. His training compels him to control the usual instinct of escape and to become an automatic machine which marches and shoots. Yet when the soldier doubts the quality of his arms, lacks complete faith in his leaders, fears that his platoon or company has lost contact with the main body and is being surrounded, then that soldier loses confidence, becomes fearful or even panicky. His already depleted energy is further abruptly

reduced. Fear exhausts more than exertion. It utilizes the nerve pathways, the metabolic processes, the muscles, as does constructive purposeful activity. Yet the indecision leads to energy wasted in motion and in inhibition, as when racing a motor of a car held back by unreleased brakes. Overwhelming fear leads to rapid heart action, to rising blood pressure, to outpouring of adrenalin counteracted by "frozen" muscles or expressed by tremors. Not only muscles but thinking processes seem paralyzed by doubt and fright.

If among industrial workers psychologic factors, such as interest in the job, relationship to personnel, rewards for work are important, they are even more so among soldiers in combat. It is well known that soldiers marching to attack are less fatigued than when they retreat even though the distance and terrain be identical. The failure of the mission meant fatigue. A major observed in a certain theater of operations that the number of patients referred into the hospital with acute combat fatigue, labeled "exhaustion" because fatigue was a prominent feature, was fewer during the period of successful attack than when our forces were in danger of being surrounded. In combat, fatigue results not from one item but the combination of exertion, deficiency and psychologic factors. The psychologic factors especially of fear, the depletions resulting from deficiencies, and the excessive expenditure of energy lead to a variety of symptoms.

#### THE MAN WHO IS FATIGUED

Before reviewing symptoms let us consider the man. For our practical concern as physicians is not with fatigue, it is with fatigued men and women. Not the exposure alone but the caliber of the exposed determines the degree of symptoms. In our discussion we may take up the physical and the psychologic aspects separately, though in life they are inseparable.<sup>4</sup>

There is a muscular quotient as there is an intelligence quotient. The Army gives every inductee an intelligence test that enables a separation into five classes from Group I (superior intelligence) to Group V (lowest group). We utilize such classification in duty assignments. Yet men are also different as to their muscular and motor power. The bodily processes—metabolic, circulatory, muscular—the sum total of which is action and stamina, are different from man to man. We vary in the capacities of our backs as in the functions of our brains. Some men can march further, lift more, and possess the resiliency to regain well being after exertion. Others fatigue more quickly and take a longer time to recuperate. Not only is there an innate difference but also age, body build and of course training may modify this difference. The Army took cognizance of the importance of age in the selection of younger men for combat only. So also in picking troops for hot climates, Circular Letter SGO No. 119<sup>5</sup> advises the selection of ' wiry men between the ages of twenty and thirty.



The psychologic factors depend upon the personality makeup. Some men possess self-confidence, accept their assignments cheerfully and endure hardships with the average attempt to dissipate dissatisfaction by humor and griping. Others start out in life with the minus sign of being tired out because of self-pity, worry, ideas of being mistreated. Energy thus expended in doubt and distrust is energy wasted. He is most fatigued who is tired of it all.

We may take a detour from our discussion of personality and fatigue to glance at the reactions of soldiers injured in combat. The decisive factor is the personality more than the injury or loss. Recently I lived with a group of amputee soldiers and officers—men wounded in combat and suffering the loss of an arm, leg or several members. The reactions of a lieutenant were typical. "Sure, I lost both hands in the grenade explosion, but I got to make the best of it. I have learned to use the prostheses (grasping device), I can write with a pencil, can type, eat, and I am learning to do more every day. I have a tough time buttoning a shirt, and tying the knot of my tie, but I'll master those. My real ambition is to learn to shoot—I love quail hunting." This officer showed no self-pity, was not lost in his tragedy but was studying salesmanship and trying to rise above his defect. So, too, men differ in their later reactions to fatigue.

As we consider symptoms and clinical states, let us keep in mind not only the stress of industry and warfare but also the qualities of the man subjected to the stress.

#### SYMPTOMS AND SYNDROMES

Guttman and Rimolditt<sup>6</sup> include the following items under the symptoms of and meaning of fatigue. The output curve of effort diminishes, psychologically, there is an attitude of boredom and loss of interest, unpleasant sensations locally such as aches and pains, and the emotional tone tends towards depression, with loss of initiative, slowness, indecision and a sense of incapacity. All of us are aware of the local distress of fatigue, tired sore eyes with blurring of vision after prolonged reading, sore, weak, aching muscles after a long march. Profound depression or apathy occurs after greater exhaustion. Such apathy was illustrated by the experience of a British officer, taken captive in the retreat to Dunkirk. He had marched with his men day and night, taking little time for rest, and subsisting on little or no food. After several days of such exhausting march he and his men were surrounded by the enemy. He surrendered automatically, too tired to observe, too tired to care. He could barely hold his head up, barely lift his feet as he trudged to a vehicle and later was transferred to a train. He took no notice of where he was being moved, fatigue made him almost entirely oblivious to recognition of time and place. He didn't seem to care. After he had rested in the prison camp and after he was refreshed by food, he became keenly conscious of his surround-

ings. He took careful note of the place, its guards, its weaknesses, and began to plan an escape. Within a short time he succeeded in the escape.

Fatigue is usually accompanied by indifference or apathy, yet the mental state will depend upon the degree of exertion and upon the nature of the cause. There is subjective grading from saturation to exhaustion, from staleness to complete inability to go on.

Likewise fatigue occurring in play may be pleasurable, in work, painful. Success or failure are important. The two partners of a foursome who come back joking and cheerful after eighteen holes are the victors, the defeated drag in, more tired. Success affords exhilaration, failure, exhaustion.

Thus, the direct effect of fatigue is local discomfort, intellectual dulling towards inattention and apathy, plus a general decrease in efficiency and performance. Such symptoms apply chiefly to industrial fatigue. Consider the soldier whose fatigue has resulted from a combination of exertion, deficiency, and fear. The soldier may exhibit symptoms not as a direct result of exhaustion but indirectly as escape mechanisms when exhaustion has broken the wall of personal defense. Like sandbags protecting the banks of the Mississippi against flood, so is the self-control that each person has built for himself. From infancy onwards we have acquired the self control that enables us to restrain cries and tears, to check trembling and running. Army training adds to this wall of self-control so that we maintain our positions despite the sound and recoil of fire, can distinguish between the true danger of a near bomb burst from the distant roar of artillery. This enables the soldier to go forward, to appraise danger and face it, to dismiss thoughts of terror, to distinguish images from reality.

Fatigue and exhaustion remove this wall of self control, as time and the elements wear away the sandbags of protection. Some soldiers, like a quiet river, move lethargically, while the pent-up emotions of others sweep over all bonds and release all manner of reactions. Like a raging river torrent which inundates the land, the emotions run riot, one cries, the other laughs, one trembles, wanders in confusion. The type of syndrome will reveal the interplay between exhaustion, the experiences, weaknesses, and strivings of the individual. Truly, every man has his breaking point, but the direction and extent of the break vary. Like glass exposed to excessive pressure which may crack in one or two main lines splinter in many directions, or blow to bits, so the reaction to exhaustion differs. In some the upset is abrupt, in others it is gradual, passing through prodromal stages toward the phase of advanced symptoms. Kubie<sup>7</sup> lists some of the early symptoms (signal of incipient breakdown) as sleep disturbances and nightmares, daytime startle states, abstracted manner, change in voice, change in daily habits, and in personality. As the condition continues, more pronounced syndromes appear.

The disorders may affect the motor apparatus chiefly the

organs, or the mental control. Thus, tremors or paralysis may dominate the picture, or a series of autonomic derangements, tachycardia, nausea, vomiting, diarrhea, represent the reaction, or acute confusion, manic behavior, stupor may set in. Braceland and Rome<sup>8</sup> list the symptoms of severe exhaustion in the Naval service as follows

- 1 Heightened irritability (startle response, night terrors, vigil state)
- 2 Autonomic nervous symptoms (tachycardia, gastrointestinal upsets, sweating)
- 3 Fatigue—a diminished capacity for work
- 4 Personality changes—depression, anxiety, panic, apathy, confusion

Among the acute nervous reactions of British soldiers in the Middle East are mentioned "shivering, stuporous states, hysterical manifestations, like deaf mutism, paralysis, or blindness"

The commonest syndrome is an acute *anxiety state*, combining motor, visceral, and mental symptoms. The anxiety is exhibited by tremors and weakness, pallor, sweating, tachycardia, sensitivity to noise, disturbed sleep, irritability. Noises startle, a remark may lead to tears or a storm of anger. Such an acute nervous reaction is not a static picture but fluctuates from day to day in response to treatment and upon exposure.

Exhaustion is not the basic cause of a true neurosis. It will, however, set in motion symptoms of an acute nervous state. Such symptoms if properly cared for clear up, yet improperly treated and under certain circumstances the acute reaction is the starting point for a chronic neurotic state. The British report of *Psychiatric Casualties*<sup>9</sup> states, "Physical exhaustion is the commonest precipitating cause of nerves." The importance of exhaustion as a factor in causing such disorders is stressed by Farrell and Appel.<sup>10</sup> "The highest admission rates (for neuropsychiatric cases) occur in troops in actual combat. In overseas theatres where there is no active combat the rates are lower than among troops within the United States. The per cent of neuropsychiatric casualties rises in direct proportion to the length of active combat duty."

#### TREATMENT

**Prevention**—Prevention is the first step, yet not always attainable. In industry the hours of work may be reduced, in warfare the situation commands the man. Then, too, though it might be advisable from the medical standpoint to relieve fighting men before profound fatigue sets in, yet from the military aspect such relief may not be available or practical. Any recommendations can be carried out only in the framework of reality situations.

Prevention and treatment may be carried out along three lines: physical, psychic and drug—or, to put it in alliterative form, muscular, mental and medicinal methods can be used.

**Physical Conditioning**—First is the selection of the physically fit, as for example the choice of lean young men for tropical service. Next is training. Toughening marches and physical drill will improve muscle action and enable the soldier to withstand the rigors of combat. Such training helps muscles and the circulation, and increases general stamina as well. Pilots are encouraged to exercise and play ping pong, swim, do calisthenics, rather than to mope, drink, and play cards. Soldiers should continue training and recreation during inactive periods. We must build the capacity for prolonged exertion.

**Mental Attitude**—A decisive element in fatigue is the mental attitude. The soldier who is absorbed in his task, who is striving for a goal, can draw upon an almost inexhaustible reservoir of energy. He who feels unhappy, mistreated, defeated, wastes his present energy and dissipates reserves. This applies equally to the man in industry.

The stamina of the soldier is closely related to his morale. The fighting man who thoroughly believes that he is fighting for his family, who has faith in his leaders, who identifies himself with "its cause," can march farther, hold out longer. So, too, the employee whose job is interesting and who feels the reward is fair will ignore fatigue. A mother nursing her sick child can keep going day and night, unmindful of tiredness because her duty is a labor of love.

We are all familiar with the picture of the young woman returning home from a hard day's work, bored, unhappy, and tired. She flops into bed, too exhausted to eat. In this state of near stupor she lies, when suddenly the phone rings and an almost forgotten but highly desired boy friend invites her to a night club. She is electrified into energy. With singing voice and elastic step she bathes and dresses. How vivacious she appears as she dances late into the night!

The soldier who is patriotic, who is imbued with a close attachment to his buddies, who is proud of his outfit, will find few tasks too hard, will develop the endurance to keep going. Confidence in the outfit, faith in its leaders, the success of the venture, all influence fatigue or resistance to exhaustion. Outfits whose men lack confidence, who have little faith in their leaders, outfits which are retreating, have a disproportionately high percentage of nervous casualties. The prospect of victory is a tonic more invigorating than vitamins.

**Medicinal Therapy**—Situations arise when even well trained soldiers inspired by splendid morale reach a stage of exhaustion, yet military exigencies demand their further action. Thus, many measures have been tried in the hope of improving physical effort, or of delaying the onset of fatigue. Hellebrandt and Karpovich<sup>11</sup> have reviewed the use of special diets, sugar feeding, high vitamins, gelatin feeding, method of changing the acid balance (alkalies, phosphates, chlorides), beverages such as alcohol, coffee, tea. They state that there is no convincing proof that special hours of eating, excess sugar, extra vitamins, gelatin, or the acid-alkali group will improve performance of an aver-

age man Quoting from these authors, "Small doses of alcohol, beverages containing caffeine, amphetamine (benzedrine sulfate) or cocoa leaves all raise the level of physical performance in the course of prolonged effort by lessening the appreciation of fatigue Items to improve energy are usually dangerous but when the emergency is acute it may be wiser to resort to the use of substances which make men temporarily immune to fatigue than to abandon the exhausted"

The army uses *benzedrine sulfate* for such emergency purpose Circular Letter No 58 SGO<sup>12</sup> says, in effect "Benzedrine sulfate is a potent 'awakening' drug It stimulates dynamic energy, postponing the desire for sleep, and enables continuation of performance beyond the point at which physical fatigue would be overwhelming It will not improve the capacities of a rested person, and will cause sleeplessness if taken near bedtime Furthermore, it may produce palpitation, excitement, undue sense of tenseness and uneasiness In a special situation when it is important to alleviate fatigue and sleepiness benzedrine has proven highly useful It is administered after the appearance of fatigue, not as a preventive The dose is 5 mg for sleepiness, 10 mg for marked fatigue This dose, 10 mg, may be repeated if needed, at intervals of not over six hours for a total of three doses"

Aside from the use of benzedrine sulfate, we urge sufficient salt intake in the tropics Circular Letter No 119 SGO (July 1943)<sup>8</sup> advocates gradual acclimatization, slowly increasing amounts of work, and the addition of free salt to the water intake

Treatment of Fatigue States with Features of a Neurosis—Despite the use of preventive measures, warfare brings exhaustion and exhaustion leads to the expression of hitherto controlled nervous reactions The rules of treatment are (1) early recognition (2) rest and sedation (3) psychotherapy

Braceland and Rome stress the need of removing a sailor from the area of duty if there are prodromal symptoms of mounting anxiety or excessive fatigue

The soldier who has been long in the front lines and whose loss of appetite, irritability, inefficiency and tremors, indicate advancing trouble, must be sent to the battalion aid station He must be removed from the sounds, dangers and hardships of front line fighting

At the battalion aid station or farther to the rear the soldier is given rest and sedation Major Hanson<sup>13</sup> relied upon amytal sedation, first large enough to enforce deep sleep for some twenty-four hours, then sufficient to provide relaxation, but also to permit the soldier to attend to minor details Before the period of deep sleep, or soon afterwards, each soldier got a bath and a full diet with ample sugar and vitamins This period of rest reinvigorated tired muscles and broke the links of the chain of anxiety Braceland and Rome mention pentobarbital sodium, seconal and sodium amytal as the safest forms for intravenous use when it is advisable to induce deep sleep After an initial intra-

venous dose, such medication might be given orally Sargent<sup>14</sup> stresses prompt approach 'The urgency of treating with adequate deep sedation an acute neurosis in a good personality starting to break down is like an urgent operation for acute appendicitis This is followed by measures to improve that patient's weight loss by a modified insulin therapy (20 to 100 units of insulin at 7 00 A M The patient is not allowed to go into coma) "

Farrell and Appel state that recovery occurred in 60 to 80 of the cases arising in combat, with the patients returning to full combat duty provided they had been regarded as medical emergencies and properly treated Circular Letter No 176<sup>15</sup> SGO entitled Early Recognition of Neuropsychiatric Conditions in the Combat Zone emphasizes selection, sedation and psychotherapy

Ross described the experience of soldiers in World War I 'During the retreat from Mons the soldiers kept going for one week The army marched and fought and dug and marched and fought and dug At the end of this period they lay down and slept for thirty-six hours Refreshed by this sleep it took the battle of the Marne in its stride "

Hurst described soldiers as "tired almost to death," "staggering as though chloroformed," who after a few days' rest were young and fresh.

**Psychotherapy**—Refreshing rest, deep sleep and good food will be psychotherapeutic in their action Yet, in some instances, the fighting man needs some explanation, reassurance, relief of a feeling of guilt. Grinker and Spiegel<sup>16</sup> provided such relief of emotional tension by encouraging the soldier to relieve his painful experiences under the influence of pentothal sodium Kubie suggests first rest and sedation, then physical measures and psychotherapy

For treatment of neurosis which has become established Kubie suggests primary measures consisting of controlled sleep plus physical restoration and psychotherapy in the form of superficial catharsis The first consideration is sleep, nourishment and some recreation, then the patient is given a chance to free himself of anxiety "Most emotionally disturbed patients try to hide their feelings When this effort fails, one sees all degrees of anxiety, with shaking, shivering, chattering, starting, dashing away to hide, sweating, vomiting, etc The patient may be lost in depression with suicidal tendencies or he may swing to wild and meaningless gaiety There may be an uncontrollable need to talk obsessively and endlessly about home and family about recent experiences, about the men who have been killed, about the conduct of officers, etc. Since human beings like to blame their troubles on superiors or on subordinates, pet hates and resentments will be heard frequently The patient should be guided to get release a feeling of guilt, relief of rage'

The average normal fighting man will respond favorably to food, sedation and psychotherapy Fatigue is reversible The

person can develop nervous symptoms from fatigue yet he will return quickly to normal when the situation is improved and when rest is provided. Many soldiers, however, do not improve sufficiently under such a program, indeed, symptoms remain chronic. What is the meaning of chronic fatigue and chronic neurotic reactions?

#### CHRONIC FATIGUE STATES AND NEUROSIS IN MILITARY LIFE

Though the fatigue state is for the most part a reversible process there are many examples of prolonged symptoms of exhaustion. Such conditions usually represent neuroses or some coexisting physical illness. Ross<sup>17</sup> interprets the prolongation of illness from fatigue states as due to two causes: (1) fear of consequences of further exposure, and (2) gain to be derived from illness. It is Ross's opinion that these symptoms represent a defense against the possibility of further damage, and that if the soldier is assured that he will not be sent back to duty, the probability of recovery is increased. "Everyone wants to be well, but everyone is not prepared to accept in all the circumstances the consequences of being well."

Fatigue is not identical with neurosis even though at a certain point both may have similar symptoms. Fatigue is temporary, neurosis is likely to be prolonged, fatigue is the product of the situation, a neurosis is fundamentally related to the personality, even if the situation has induced active symptoms, fatigue is reversible, but neurosis is deep set.

What about the common ground between them? (1) Fatigue may induce neurotic symptoms—the tremors and anxiety constitute but a resemblance. All that glitters isn't gold, all who tremble aren't neurotics. (2) Fatigue may bring a true neurosis into evidence—activate it, as it were. Many a potential neurotic controls his symptoms by the effort of will power, by precautions, by activity. Busy and absorbed, he may produce effectively. A soldier may be struggling with the conflict between continuing to fight on or retreating. His sense of duty, his feeling for his buddies, his fear of censure will keep him in the fight. But once exhaustion has set in, this control is weakened, once he is hospitalized, the conflict is decided in favor of escape. Not that the soldier needs a conscious decision that this illness is a door to escape. Rather the mechanisms of self pity and introspection are awakened by the palpitation and the pain, fear of bodily failure, of serious disease is set in motion so that the soldier becomes a timid, trembling, tearful, and dependent patient. As long as he was going on and on, buoyed by the force of the group, stimulated by morale, he remained a good soldier—but once this link was broken he becomes a sick patient—all the latent fears, guilt, anxiety have come to the fore.

What about the conscious element, the factor of gain, of escape? Some believe that such gain, a conscious element is the effective force behind prolongation of symptoms. On the surface this appears so. Yet

one can only go as far as to say that the conscious factor reinforces the unconscious. The unconscious is basic, primary, develops out of the situation, the conscious is secondary. Yet its reinforcement adds much to the effectiveness of this force in maintaining invalidism.

The treatment of the true neurotic requires more time, a different setting, and usually, more involved techniques than mere rest and sedation. Such soldiers may have to be evacuated to the zone of the interior (the United States) away from the noise of bombers, away from fear of further exposure. Indeed, so powerful is this fear in some patients that they are relieved only when separated from service. Along with such evacuation comes intensive psychotherapy, analysis of the situation, free discussion, plus guidance, suggestion (see *The Mind of the Injured Man*<sup>18</sup>).

#### DIFFERENTIAL DIAGNOSIS BETWEEN COMBAT FATIGUE AND FATIGUE SECONDARY TO ILLNESS

As a rule, the fatigue states in combat are the result of the combined factors of exertion, deficiencies and fear. Yet often in civilian life and during training the patient emphasizes fatigue without obvious external factors. Physical disease can produce fatigue and nervous symptoms as well as the combat situation. Let us briefly discuss several common maladies.

**Tuberculosis**—In industry and less frequently in the armed forces (routine chest films) progressive fatigue ushers in pulmonary tuberculosis. Before cough, chest pains and obvious fever develop the patient may complain of tiredness, weakness, become apathetic or irritable and fail to carry out his duties.

**Addison's Disease**—Tuberculosis of the adrenals produces fatigue and this may be an important and prolonged symptom. A 38 year old soldier was inducted into the Army and sent to Florida for his basic training. During the earlier period of marching he complained of weakness. Later he "fell out at drill," stating he was too tired. He was at first suspected of being a "goldbrick." His fatigability grew worse. The soldier noticed that his skin was turning dark but was told that it came from the Florida sunshine. Weeks later he developed nausea and vomiting. He was therefore hospitalized and found to have pigmentation of the mucous membranes of his mouth, low blood pressure and chemical evidence pointing to Addison's disease.

**Blood Dyscrasias and Pernicious Anemia**—A lieutenant had difficulty in marching, his feet grew tired. Then he developed shortness of breath. Weeks later came numbness and tingling. During the earlier phase of this illness his appearance was one of good color and the true nature of the illness was not suspected. When the tingling was followed by unsteadiness in walking a neurological revealed evidence of combined sclerosis of the cord. Blood



and analysis of the gastric juice (achlorhydria) furnished the answer—pernicious anemia

*Heart Disease*—Fatigue on walking may be the prologue to the drama whose epilogue is decompensation. Leg weakness, then shortness of breath may be followed by angina or a true coronary attack. In the early phase fatigue may be the presenting symptom.

*Malignancy*—It is not rare for malignancy to start out as fatigue and then to give local evidence of its presence. A patient complained of weakness and nervousness, for which he was referred to a neuropsychiatric clinic. As he did not respond to psychotherapy, but instead lost weight, the psychiatrist requested a chest film (to rule out tuberculosis). The chest x-ray showed numerous coinlike rounded shadows which were interpreted as due to metastasis. Months later, the autopsy revealed that the primary source of this malignancy was a microscopic teratoma of the testes.

*Other Diseases*—Enough has already been mentioned so that we must keep in mind the possibility of inherent disease rather than the situation. In passing we can mention hyperthyroidism, undulant fever and hypertension as conditions to be considered. Then, also, endogenous depression may start out with weakness, leg tiredness, loss of appetite, and nervousness. Muscles are messengers of the mind and sometimes droopy posture and dragging legs will precede gloomy thoughts in the progress of symptoms of depression.

#### TREATMENT OF FATIGUE IN CIVILIAN AND INDUSTRIAL LIFE

Here we must first rule out physical disease, then evaluate the occupational situation. Is the fatigue due to excessive hours or boredom, is it due to physical exertion or unhappiness? In therapy we must remember the all-important influence of the mental attitude. It is good business as well as good medicine to furnish an incentive, to instill team spirit, to provide pleasant environment and remove as many industrial hazards as possible. Excessive cases of fatigue reflect upon management as well as the men fatigued.

#### CONCLUSION

Fatigue and exhaustion constitute a significant problem in war and in peace. In civilian industry fatigue is a symptom of excessive expenditure of energy without sufficient time for rest, results from physical disease, or is induced by a mental attitude of disinterest or dislike. Among fighting men these factors plus a succession of harrowing experiences, plus deficiencies of sleep and diet, and especially the influence of fear, lead to exhaustion states. As a rule such fatigue states are reversible. However, not all symptoms are the direct result of fatigue. Some arise as release phenomena, and these may persist especially if a marked potentiality to neurosis is awakened. The value to the ego of the escape from danger reinforces unconscious symp-

toms A careful differential diagnosis is essential Treatment along muscular, mental, and medicinal lines is indicated

## BIBLIOGRAPHY

- 1 Sayers, R R Major Studies of Fatigue War Med., 2 786 (Sept.) 1942
- 2 Hurst, A Medical Diseases of War Baltimore, Williams & Wilkins Co., 1941
- 3 Pyle, E. Here is Your War Infantry J., July 1943
- 4 Fetterman J L The Correlation of Psychic and Somatic Disorders J.A.M.A., 106 26 (Jan ) 1936.
- 5 Circular Letter No 19 Acclimatization of Troops in Hot Climates Surgeon General's Office, July 1943
- 6 Guttman, E. and Rimolditt, J Fatigue and Effort Syndrome. Mental Science, 87 349 (July) 1941
- 7 Kubie, Lawrence S.. Manual of Emergency Treatment for Acute War Neuroses. War Med., 4 582 (Dec ) 1943
- 8 Braceland Comdr F J and Rome, Lt H P Anxiety and Fatigue Connecticut State M J., 7:827 (Dec.) 1943
- 9 Psychiatric Casualties in the Middle East Forces Army M Bull., 66 113 (April) 1943
- 10 Farrell, Lt. Col M J and Appel Capt J W Current Trends in Military Neuropsychiatry Am J Psychiatry 101 12 (July) 1944
- 11 Hellebrandt, F A and Karpovich P V Fitness, Fatigue and Recuperation. War Med., 1 745 (Nov ) 1941
- 12 Circular Letter No 58 Benzadrine Surgeon General's Office Feb 23 1943
- 13 Hanson, Major F Personal communication.
- 14 Sargant, W Physical Treatments of Acute Psychiatric States in War War Med., 4 577 (Dec.) 1943
- 15 Circular Letter No 176 Early Recognition and Treatment of Neuropsychiatric Conditions in the Combat Zone. Surgeon General's Office, Oct. 20 1943
- 16 Grinker Lt. Col. R. R. and Spiegel, Maj J P Brief Psychotherapy in War Neuroses. Psychosom Med., 6 123 (April) 1944
- 17 Ross, T A. War Neuroses. Baltimore, Williams & Wilkins Co., 1941
- 18 Fetterman, J L. The Mind of the Injured Man. Chicago Industrial Medicine Book Co., 1943

PHYSICAL MEDICINE IN MEDICAL REHABILITA  
RDON M. MARTIN, M.D.

GORDON M MARTIN, MD\* AND FRANK H KRUSEN, MD, I

PHYSICAL medicine has a vital role to play in the rehabilitation of individuals disabled by many nontraumatic or nonsurgical conditions. The vast majority of recent work and programs for rehabilitation has emphasized the rehabilitation of persons suffering from war wounds and industrial injuries. Less attention has been given to the less spectacular, but often just as disabling, medical conditions. Many common medical conditions observed in civilian and military practice are associated with long periods of convalescence and loss of productivity. In war years, society is vitally interested in the rehabilitation of the disabled, and a vigorous program of rehabilitation is in power. The program aims to have everyone, whether physically disabled or partially disabled, producing at maximal capacity for the welfare of the group. However, in peacetime, when manpower is not so scarce, the problem of an individual disabled so that he cannot support himself is of less interest to society. A person disabled by chronic disease receives medical care, food and shelter. Often, a longed-for palliative treatment is given with no attempt at a vigorous physical rehabilitation program aimed to prepare the disabled one for a self-supporting job, and little is done by industry to find a place for such an individual. In many states, compensation laws have discouraged and even prohibited the employment of physically handicapped persons.

The recent war years have shown that many partially disabled individuals can be fitted for a productive occupation suitable to the specific disablement. Industrial planning and placement boards are finding the job opportunities and means of decreasing periods of hospitalization and absence from active duty and military service (Grant,<sup>4</sup> Rankin and Barton<sup>6</sup>). The aims of well-organized over-all medical rehabilitation programs must be to reduce convalescence to a minimum and to follow through with the treatment program of the individual until he attains his maximal functional capacity. These programs should continue to expand so that postwar rehabilitation and reconditioning programs will be available in all hospitals and clinics for private patients as well as patients on industrial and other medical insurance programs.

Physical medicine often can serve as a valuable part of the program

\* Director of Physical Medicine, The University of Kansas Hospitals, Kansas City, Kansas

† Head of the Section on Physical Medicine, Mayo Clinic, Rochester, Minnesota

that aims to hasten the return of a disabled individual to his maximal functional capacity. Physical medical measures started early, prescribed carefully, and administered expertly have been found to shorten convalescence, reduce the period of hospitalization and minimize the expense to the patient and loss of hours from the job. The physical medical procedures should be carefully coordinated and integrated with the other types of treatment that are indicated for each individual.

#### PHYSICAL MEDICAL PROCEDURES

Principally, physical medical measures include the familiar triumvirate of heat, massage and therapeutic exercise. These may be used alone or in various combinations and in various forms to achieve the desired results. The fundamental physiologic reactions of the body to the various agents must be kept in mind if these agents are to be used properly and to the best advantage to help correct the abnormalities of the individual patient.

**Heat**—Heat, in general, can be used to increase circulation, relieve pain, increase local metabolism and relax tense muscles. The most effective means of applying heat locally to a region are (1) luminous heat lamps or bakers, (2) short wave diathermy, (3) hot paraffin, (4) hot soaks and (5) hot wet packs. General heating of the body is best accomplished by the hot tub bath (water temperature 100° to 106° F) or by use of a hot humid air cabinet.

**Massage**—Massage can be used either for sedative or stimulating effects. Stroking and kneading massage will improve venous and lymphatic flow and may be used to stretch intermuscular connective tissues. Friction massage can aid in stretching and loosening scar tissue and adhesions. Best results from massage are obtained when it is administered by an individual skilled in its application. Usually, the effects of massage are enhanced by preliminary application of heat for at least twenty or thirty minutes.

**Exercise**—Therapeutic exercise is undoubtedly the most important part of the physical medical phase of the rehabilitation and reconditioning programs for the majority of patients. The type and the amount of exercise will vary the condition being treated. Active exercise is used to improve muscle tone and muscle strength. Assistive exercise is used to increase range of motion. Passive exercise is used when it is desirable to prevent contractures, maintain muscle sense and aid circulation in a paralyzed extremity.

With therapeutic exercise established as the keynote of the physical medical phase of rehabilitation, it is obvious that complete cooperation of the patient is a primary requisite for successful carrying out of the program. The physicians, nurses, attendants and physical therapists are all responsible in helping the patient to realize his own responsibility for obtaining the maximal benefit most rapidly from the exercise program which is prescribed for him. A constantly changing program of

graduated exercises with definite goals to be attained must be prescribed and carefully supervised

**Occupational Therapy**—In addition to the physical therapeutic procedures just considered, occupational therapy provides another approach to the rehabilitation programs. Occupational therapy is a part of the physical medical program. It includes the use of prescribed work in the field of arts and crafts and recreational activities done by the patient as an aid in improving function of a part, or parts, as a diversional activity and morale builder, and, in some instances, as a part of a prevocational training program. By means of selected activities that interest the patient and are prescribed with definite aims in mind, the patient is further aided in feeling his own responsibility for attaining a maximal recovery. Unfortunately, at present there is a shortage of trained and competent occupational therapists. Physicians are not cognizant of the values, technics, indications and methods of prescribing occupational therapy for their patients. There is a lack of well-organized and accessible occupational therapy departments in most civilian and military hospitals. With more technicians being trained and the medical profession gradually learning about occupational therapy, it can be anticipated that the occupational therapy portion of physical medicine will, in the future, play a more prominent role in the rehabilitation programs for civilian, industrial and military patients.

#### MILITARY RECONDITIONING PROGRAMS

The Army general hospitals, and more especially the hospital services associated with the Army Air Force rehabilitation and reconditioning programs, have made extensive use of daily calisthenics beginning while the patient is still in bed (Rusk<sup>7</sup>). Generally two ten minute periods daily are set aside for the calisthenics. After the patient is able to pass an exercise tolerance test, described by Karpovich, Starr and Weiss,<sup>6</sup> based on a return of pulse to a rate of below 100, the pulse being taken one minute after mounting a 20 inch step twelve times, in thirty seconds, he is graduated to a more strenuous exercise program. In the more advanced classes the patient spends thirty to forty-five minutes twice daily in calisthenics, games and guerilla exercises that are conducted outdoors. The most advanced classes in the reconditioning programs include two forty-five minute periods of outdoor games, exercises and cross-country running and sprinting. This program has been found definitely to shorten the period of hospitalization and lower the incidence of relapses among patients suffering from respiratory infections including pneumonia.

#### PREVENTIVE PHYSICAL MEDICINE

Many years ago it was found that breathing exercises that were started soon after major surgical procedures lowered the incidence of

*postoperative pneumonia* These exercises are now used routinely in some form in most hospitals. Sometimes inhalation of carbon dioxide and oxygen is used as an added stimulus to the deep breathing. It is well known that to be of value the exercises must be done several times daily under the supervision of a nurse or attendant trained for this work.

The medical practitioner is still too frequently called to see patients suffering from *pulmonary embolism*. Several prophylactic measures have been used extensively. Dicumarol has proved to be of considerable value but requires careful observation and frequent determinations of the prothrombin time. Simple graduated exercises that are started at the same time as the breathing exercises have been found to be an aid in the prevention of pulmonary embolism. Wangenstein<sup>9</sup> has emphasized the importance of constant active motion of the feet and toes during waking hours in obviating stagnation of venous blood in the legs. He expressed the opinion that this is an important factor in preventing thrombosis and embolism and in preparing the elderly surgical patient for becoming ambulant early.

A suggested group of simple exercises that can be started while the patient is still in bed could include some of the following:

- Exercise 1 Flexion and extension of toes. Repeat five to ten times.
- Exercise 2 Flexion and extension of ankle. Repeat five to ten times.
- Exercise 3 Circling of feet. (Circumduction with motion at ankle and midtarsal joints.) Repeat five to ten times.
- Exercise 4 Quadriceps setting. Tensing of quadriceps muscles in extension position of knee. Hold for a count of five. Repeat five to ten times.
- Exercise 5 Flexion of knee and hip, sliding foot on mattress toward the buttocks. Repeat five times.
- Exercise 6 Squeeze thighs together, then abduct them until feet are 12 inches (30.48 cm) apart. Repeat five times.
- Exercise 7 Gluteal setting. Squeeze buttocks together. Hold for count of five. Repeat five to ten times.
- Exercise 8 Deep breathing. Protrude abdomen (diaphragmatic breathing). Repeat five times.
- Exercise 9 Deep breathing. Raise thorax. Retract abdomen (thoracic respiration). Repeat five times.
- Exercise 10 Clench fist. Flex and extend elbow five to ten times.
- Exercise 11 From neck firm position. Draw arms forward to side of head. Then return to firmly retracted position against bed. Repeat five to ten times.
- Exercise 12 Flexion of neck. Chin toward thorax. Repeat five to ten times.

A minimum of five minutes twice daily should be spent in doing definite exercises. The exercises should be selected by the physician. Overfatigue must be avoided. A persistent elevated pulse rate follow-

ing exercises is an indication of overexercise. These or similar exercises are of value in aiding circulation by the action of the muscle on the veins. Muscular tone is improved and the commonly seen conditions of flabby, weak muscles and atrophy of disuse are minimized. A ward attendant, nurse or nurse's aid can be trained to supervise the patient in the prescribed exercises.

#### PHYSICAL MEDICINE APPLIED TO MEDICAL DISEASES

**Arthritis**—Rheumatoid arthritis involving peripheral joints, spinal column and the muscle is a commonly seen, chronic, disabling medical condition that affects both men and women during early adult life. Medical management should include a thorough search for, and eradication of, foci of infection, and the judicious use of salicylates, a trial of some type of arthrotropic or autogenous vaccine, adequate rest, well-balanced diet, vitamin supplements, a trial of large doses of vitamin D and possibly the intravenous use of gold salts.

Physical medical measures are used to improve peripheral circulation, relieve pain, lessen muscular atrophy, prevent deformity and improve articular function. The importance of daily use of physical measures cannot be overemphasized. Applications of heat for half an hour once or twice weekly is mentioned only to be condemned as a valueless procedure. Simple physical measures that the patient can use daily at home, in addition to what professional treatment he can afford or is available, should be included in the physical medical program.

Heat can be applied locally for thirty minutes daily by means of luminous heat lamp, melted paraffin ( $120^{\circ}$  to  $130^{\circ}$  F), or short wave diathermy. Generalized bodily heating in a hot tub bath with a water temperature of  $100^{\circ}$  to  $105^{\circ}$  F for twenty minutes should be used two or three times weekly. This raises bodily temperature to about  $100^{\circ}$  to  $101^{\circ}$  F and is thought to aid the bodily defenses against the arthritis. Bodily metabolism is increased and the blood picture shows an increased leukocyte count.

Application of heat should be followed by a stroking and kneading massage especially to the muscular tissues around the involved joints. This aids in maintaining circulation through the muscles, stretches intramuscular connective tissue that may be involved in the arthritic process, and helps to prevent atrophy. Acutely inflamed joints should be avoided in the massage.

Exercise varies from minimal active and passive motion in acutely involved regions to vigorous active and assistive exercise in the chronic stages or in "burned out" arthritis with varying degrees of limitation of motion. Routine exercises can be supplemented by activities in occupational therapy that are used to improve function of joints as well as to provide mental diversion. When the arthritic process involves the spinal column, the exercise program also must include postural training as well as intensive exercises to maintain or improve

expansion of the thorax. Here again, as with the use of heat, the prescribed exercises should become a part of the patient's daily life, they should be done regularly and as often as prescribed by the physician, and done with the same regularity as the individual takes internal medications.

**Poliomyelitis**—The physical medical management of poliomyelitis probably results in the best final functional results of any type of treatment that is used. During the acute stage with painful, tender muscles, hot packs tend to produce considerable symptomatic relief. The patient is positioned in bed with a firm mattress and foot board in such a way as to prevent overstretching of weakened muscles and lessen the tendency to deformities. Passive exercise is started early. Careful manual muscle re-education techniques are used to obtain maximal functional efficiency of all the muscles that are able to contract. The purpose of the careful muscle re-education is to encourage the use of weak muscles and discourage the use of stronger muscles which the patient naturally tends to substitute to carry out an action. The patient can be taught to relax an antagonist muscle whose contraction tends to interfere with the action of a weakened agonist or prime mover. Frequent observation during the recovery period, which may last many months, will guide the patient in the proper use of his muscles as function returns. Deformities can be observed in their incipient stage and often can be prevented from resulting in structural changes.

**Vascular Diseases**—Thrombo-angitis obliterans is a chronic disabling disease that usually occurs during the most active and productive years of a man's life. Here again, as in the case of arthritis, physical medicine serves as an adjunct to medical and surgical procedures that make up a successful treatment program. In the early stages, considerable symptomatic relief may be obtained by use of a Sanders oscillating bed for several hours daily. This may be of value in relieving pain and improving circulation by means of passive vascular exercise. Allen and Kvale<sup>1</sup> have pointed out that it never has been definitely proved whether or not the Buerger-Allen postural exercises improve peripheral circulation. However, theoretically, the physiologic effects should be similar to those obtained by the use of the oscillating bed.

In cases of thrombo-angitis obliterans, heat, which is used for its vasodilating effect should be applied to a distant part. Brown and Allen<sup>2</sup> have devised an electrically heated sleeve that can be left on an arm for many hours, and it has been shown that this application of heat will result in vasodilatation of the peripheral vessels in the other extremities. Bennet, Hines, and Krusen<sup>2</sup> have shown that short wave diathermy applied under the lumbosacral region results in a vasodilatation in the lower extremities. De Takáts and Miller<sup>3</sup> have found that use of the ordinary luminous heat baker over the abdomen and upper thighs is a simple, safe and effective method of applying heat to cause vasodilatation in the lower extremities. Heat applied locally to the in-



volved part may increase pain and hasten the tendency to destruction of tissue and gangrene by increasing metabolism of the part with an inadequate blood supply. Contrast baths and the application of cold should be avoided.

**Tuberculosis**—The long period of convalescence can be made more tolerable for the patient if well-planned occupational therapy activities are arranged. Productive activity is the best morale builder. Activities are available that require a minimum of physical exertion and yet provide excellent diversion so that a more relaxed type of rest program is attained. Ultraviolet light treatment or heliotherapy for patients suffering with tuberculosis of joints and certain patients with pulmonary lesions probably is not used enough in this country. This form of treatment forms an important part of the treatment programs for tuberculosis as outlined by Rollier and other European physicians.

**Cerebral Palsy**—It is becoming more generally apparent that much can be done for the many patients with spastic paralysis who have a nearly normal or superior mentality. Physical medical procedures carried out for a period of many months or years often will enable these patients to become much more efficient with improved muscular control and coordination. Certain surgical procedures are often indicated as part of the over-all treatment program.

Heat in the form of heat lamps, warm baths, or warm pools and, at times, combined with a slow stroking massage for its sedative and relaxing effects will be of benefit in reducing the tightness in the hypertonic muscles. Specialized exercise again is probably the most important single physical medical measure. A certain amount of voluntary relaxation can be learned. Rhythmic exercises, beginning with gross movements, are mastered first. Later, finer movements are learned. Progress will be slow. It may even be hindered by proceeding too fast. More special schools for early treatment of these patients in the pre-school years are needed. More technicians especially interested and trained in helping these patients are needed.

### CONCLUSIONS

Physical medicine can play a vital role in the rehabilitation and reconditioning programs that should be made available to all patients suffering from disabling medical conditions. Exercise reconditioning programs started while the patient is still in bed will shorten hospitalization and convalescence in cases of respiratory infections, including pneumonia. More prolonged rehabilitation programs in which physical medicine takes a prominent part are being planned for patients suffering from the various types of arthritis, tuberculosis, poliomyelitis and cerebral palsy. The Baruch Committee with an active subcommittee on rehabilitation is doing an important work in encouraging and coordinating the various phases of physical medicine with both the industrial and military rehabilitation and reconditioning programs. More



## NUTRITION IN REHABILITATION

TOM D SPIES, M D, F A C P \*

MAN's existence is literally a struggle for food. From conception to death he is beset with impediments to good nutrition. Throughout life many conditions may arise to prevent his having an adequate intake of essential nutrients, and he is subject to many diseases that interfere with their absorption or utilization. When, for any reason, deprivation of nutrients occurs, protective mechanisms within the body serve to compensate for a depletion of nutrients, but if the deprivation becomes protracted, these mechanisms eventually fail and signs of bodily derangement begin to appear. Symptoms, such as pellagrous glossitis or dermatitis, beriberi neuritis or beriberi heart, cheilosis or the ocular symptoms of riboflavin deficiency, scorbutic hemorrhages or gingivitis, may appear singly or in combination. They are, however, but prominent presenting symptoms of what we have come to call nutritive failure †. In order to rehabilitate the person with nutritive failure,

---

University of Cincinnati Studies in Nutrition at the Hillman Hospital, Birmingham, Alabama. From the Department of Internal Medicine, University of Cincinnati.

The tremendously heavy expenses of the general nutrition study have been borne by grants from a number of philanthropic persons, foundations and commercial concerns, without which this study could not have been made. The necessary expense of frequent observations of these patients in their homes and in the clinic has been defrayed by grants from the John and Mary Markle Foundation and from Lever Brothers.

We are indebted especially to Mrs. Jane M. Mann for most of the nursing care and to Mrs. Merle S. Babb and Mrs. Stephen Dill, social workers, for the follow-up work in the homes of the patients.

\*Associate Professor of Medicine, University of Cincinnati, Cincinnati, Ohio, Director, Nutrition Clinic, Hillman Hospital, Birmingham, Alabama.

†The term "nutritive failure" perhaps means different things to different physicians. It is used in our clinic to describe a variable clinical picture and does not have a specific physiologic connotation. It does not indicate why the nutrition has failed but simply that it has failed.

Our work has convinced us that many times the physician cannot determine at once the physiologic basis of the nutritional insufficiency, and by the use of this term he can describe briefly the clinical picture without knowing the precise causation. The term has become so commonly entrenched in our clinical usage that it does not seem wise for us to restrict it or to change it.

For the sake of clarity, the various disturbances and mechanisms which create a picture of nutritive failure we often describe separately. We can see pellagrous dermatitis or glossitis, beriberi neuritis or beriberi heart disease, scorbutic hemorrhages or gingivitis, cheilosis or the ocular symptoms of riboflavin deficiency as present symptoms arising as a response of the body to a long-continued deprivation of certain nutrients in food. Hence, nutritive failure is a more inclusive term than pellagra, beriberi, scurvy or riboflavin deficiency in that it connotes varying degrees of mixed deficiencies operating simultaneously.

we must remove, whenever possible, the causative factors and apply therapy that will not only correct the specific deficiency disease but will also restore completely the patient's nutritional status

Primary malnutrition occurs as a result of failure over a period of time to eat a diet which is adequate in all nutritive respects. Secondary malnutrition occurs when any disease or diseases interfere with the orderly processes of nutrition. It is not sufficient that a person have access to adequate food. It must be properly prepared and sufficient amounts of all the necessary constituents must be ingested and absorbed before the body can utilize them. Any illness may interfere with the natural and powerful instinct which urges us to obtain food. Claude Bernard has emphasized the fact that "all vital mechanisms, however varied they may be, have but one object, that of preserving constant the conditions of life in the internal environment." Normal nutrition constitutes the *sine qua non* of this mechanism. Without an intake of essential nutrients sufficient to meet the body's needs, all stabilizing forces eventually fail. Diseases may interfere with the proper assimilation and become an effective barrier between food and the health of the body. Then nutritional disaster comes.

During the past two decades numerous surveys of the diets of various population groups in the United States have shown that the nutritional quality of their diets left much to be desired. Little was done about it, however, until the tremendous withdrawal of young men from the farms and factories into the armed forces and the enormous production of material for war required the employment of thousands of new workers. This urgent need for manpower stimulated interest in the health and welfare of workers. Realizing the importance of nutrition in maintaining health, many physicians, nutritionists and nurses directed their efforts toward improving the feeding of industrial workers and in educating the public as to the rudiments of a satisfactory diet. The results are gratifying, but there is still much to be done. Even if it should come to pass that our knowledge of nutrition be applied in a fully effective manner toward maintaining health, the fullest benefits of this knowledge cannot be realized until it is applied toward persons who are now unable to work because they are debilitated by nutritive failure. Up to this time, however, comparatively little has been done on this problem. It is true that food has always held a place in rehabilitation programs, but its use has often been so haphazard that it was not fully effective. The vigorous young science of nutrition is constantly bringing new and valuable information. Our studies have led us to believe that the scientific and judicious application of this information can rehabilitate many persons.<sup>1 2 3</sup>

We are convinced that there is in some areas a vast resource of potential manpower among persons debilitated by malnutrition. We believe that not only are there countless persons debilitated solely by malnutrition, but that in many persons debilitated by other diseases

the nutritional status is so impaired that it is retarding their recovery.<sup>4</sup> Many of these persons have been incapable of any productive effort for years, and often they are dependent upon their families or upon social agencies. The loss of manpower attributable directly or indirectly to malnutrition is far greater than it need be. This is partly due to the fact that few physicians realize the number, the variety and the seriousness of the nutritional disorders to which man is subject or the care and skill necessary to keep human beings well nourished so that they can maintain their place in the intensive production that prevails in this country. It is due also to the fact that many physicians fail to recognize nutritional deficiencies, to apply proper therapy, or to continue treatment until the patient is fully restored to health.

Studies of nutritive failure in Ohio and in Alabama over the past fourteen years have shown us that it frequently follows diseases of the alimentary tract, surgical operations of various kinds, infections, pregnancy and lactation, neoplasm, endocrine disorders, congestive heart failure, long continued deep x-ray therapy, severe anemia and hemorrhages, diabetes, allergic states, and similar disorders. Pregnancy and lactation are very influential in precipitating the clinical manifestations of deficiency diseases where malnutrition is endemic. Likewise, we have found that in a person whose nutrition is such that little or no margin of safety exists, surgical operations and long-continued illnesses are much more of a burden than they are in well nourished persons.

From my fourteen years of study I have developed a concept of the relationship of organic disease to secondary malnutrition: the individual who has had a satisfactory diet prior to illness develops secondary nutritive failure only when the illness is severe or prolonged, whereas a person who has been on a deficient diet for many years will fall into nutritive failure with the most trivial illness. Accordingly, the degree of secondary nutritive failure is determined by the initial state of nutrition and the degree of extraneous organic disease.

It is apparent from these many years of work that nutritive failure exists first in a prodromal stage. The final disturbances occur after biochemical changes interfere with cellular function. Long after the biochemical changes first appear, they may become translated into morphological lesions which we will eventually be able to recognize as the fingerprint of the deficiency diseases or syndrome. Our studies<sup>4</sup> indicate that secondary malnutrition of a serious nature is more prevalent than any survey would indicate at any given time.

The practicing physician has been overwhelmed by an avalanche of technical material far too great for him to crystallize and use in an orderly fashion. This has resulted in the treatment of the acute stage of nutritive failure for a short time, but the recuperative stage has been neglected. The result has been that the patient has drifted through an unnecessarily long period of convalescence. Needless relapses have been far too common. The purpose of presenting the following facts

is to stress the need of accurate diagnosis and proper therapy throughout convalescence as necessities in rehabilitation following nutritive failure.

### DIAGNOSIS

Of great importance in making a diagnosis and instituting therapy is information in regard to the patient's previous and present dietary, his economic status (which almost invariably affects the quality of his diet), all the other predisposing factors which might have precipitated his nutritive breakdown, and his symptoms and the time of their onset. This can best be done by the conservative interpretation of data obtained from a careful medical and dietary history and a complete physical examination. In collecting such data, no outline is satisfactory in every detail for every patient. Nevertheless, we have found certain forms helpful. These forms are described in detail in a recent publication.<sup>3</sup>

We suspect nutritional deficiencies in the following groups

1 *Those who are indigent* Such persons seldom have enough money to buy all the foods needed for an adequate diet. Many of them have subsisted for years on high carbohydrate foods, such as bread, cereals, dried vegetables, and sugars—foods which are relatively inexpensive. Their diets usually contain far too little milk, dairy products, meat protein, green vegetables or fruit. Consequently their diets are low in protein, minerals and vitamins. Many such persons gradually lose their appetites and voluntarily reduce their food intake until even their calorie intake is inadequate.

2 *Persons with histories of erroneous dietary habits or food idiosyncrasies* Such persons frequently eat unbalanced diets deficient in some of the essential nutrients.

3 *Persons with organic diseases or infections which may interfere with the ingestion or utilization of food* Another too frequent cause of nutritive failure of a patient in this group is the therapeutic diet sometimes prescribed by the physician for the treatment of some specific disease. Although all therapeutic diets are not necessarily inadequate, we frequently see patients who develop nutritional deficiencies as the result of eating a diet prescribed for therapeutic purposes. We suggest that the physician carefully check the therapeutic diet he prescribes for each individual to see that it supplies the foods necessary for an adequate diet. If the restrictions are such that the foods permitted do not supply adequate amounts of the essential nutrients the diet should be supplemented with the nutrients in which it is deficient.

4 *Pregnant and lactating women and persons whose physical exercise is increased* In such persons the requirement of all the nutrients is increased and unless their intake of nutrients is likewise increased their nutritional status is almost certain to become impaired. Too often the food intake is increased by adding additional calories in the form of fat and carbohydrates and the diet becomes unbalanced. It is essential to increase the supply of all the essential nutrients, and if this cannot be done by food alone it should be done by supplementing the diet with nutrients in the form of synthetic substances or concentrates.

5 *Persons who are chronically addicted to alcohol* Such persons often substitute alcohol, which contains no nutrients other than calories, for food. If however a liberal, well-balanced diet is eaten deficiency diseases are not likely to develop even when large amounts of alcohol are ingested.<sup>4</sup>

In a patient in any of these groups, we suspect a developing nutritional deficiency. The early symptoms of nutritive failure include loss of weight and strength, headaches, dizziness, burning sensations of the skin in various parts of the body, roughness and dryness of the skin, burning of the eyes, blurring of the vision, lacrimation, photophobia and night blindness, burning and cramping of the stomach, burning of the tongue and lips, redness and swelling and ulceration of the tongue and mucous membranes of the mouth, increased salivation, diarrhea, burning and cramping of the feet and legs, central nervous system disturbances, which include insomnia, general nervousness, loss of memory, apprehension and hypersensitive emotional reactions.

The diagnosis of vitamin deficiency diseases is made only in the presence of one or more diagnostic lesions. Pellagra, for example, is diagnosed only in the presence of characteristic oral mucous membrane lesions or dermal lesions, beriberi only in the presence of nutritional neuritis, riboflavin deficiency only in the presence of cheilosis or typical ocular lesions, scurvy only in the presence of characteristic gum lesions or perifollicular hemorrhages.

While we perform many *laboratory tests* in our clinic, they are not, in themselves, diagnostic of deficiency states. The results of such tests, however, when correlated with the information gained from the physical examination and the medical and dietary history, are often helpful in making a diagnosis. Although they are not always practical for use by the practicing physician, facilities for some of them might be available to some physicians. We have gained useful information from various laboratory tests which include the determination of the amount of hemoglobin, red blood cells, and the packed cell volume, serum protein and albumin determinations by the Kjeldahl technic, ascorbic acid determination on plasma<sup>6</sup>, slit lamp and biomicroscopic examinations of the capillaries in the conjunctiva and cornea, the B.E.S. test,<sup>7</sup> the colorimetric method of detecting small quantities of abnormal pigments in the urine, urinary excretion tests for thiamine<sup>8</sup> and niacin<sup>9</sup>, determinations of riboflavin<sup>10</sup> and pantothenic acid<sup>11</sup> in the blood, microscopic examination for Vincent's organisms, staphylococci and streptococci in smears taken from mucous membrane lesions in the mouth, tests for hydrochloric acid, pepsinogen, and rennin in the gastric contents before and after histamine injection, and in some special cases we determined the presence or absence of the intrinsic factor of Castle.

Sufficient stress cannot be placed on the importance of searching for *mixed* deficiencies. Too often a diagnosis of a single deficiency is made, and therapy is directed toward the restoration of a single nutrient. Deficiencies rarely, if ever, exist singly. The correction of a single predominating deficiency may give temporary relief, but it will not restore completely the patient's health nor maintain him in an optimum state of nutrition. Such a procedure may, moreover, precipitate signs & symptoms of other deficiencies.

## TREATMENT

The dietary treatment of patients with deficiency disease, whether they are in bed at home or in the hospital or whether they remain ambulatory, is based on the principles of good nutrition. The diet must contain adequate amounts of protein, calories, minerals and vitamins. It must be remembered, however, that the nutritional stores of the body are likely to be severely depleted. Accordingly, the diet must supply much more than normal amounts of the essential nutrients. Therefore, the recommended diet should supply 3000 to 4000 calories, 120 to 150 gm of protein, and liberal amounts of minerals and vitamins. The type of food prescribed and the form in which it is given depend entirely upon the ability of the patient to ingest and retain food. Frequently the patient's desire for food is absent, and he has to be persuaded to eat. In the severely ill patient, the mouth and tongue may be so sensitive that only soft or liquid foods can be tolerated, and highly seasoned or acid foods must be avoided. In some instances only a small amount of food can be taken at one time, and it is necessary to give small feedings at frequent intervals. As the patient improves, semisolid and solid foods can be given. In all cases with diarrhea, solid foods should be added as soon as possible. In the dietary treatment of deficiency diseases, we have found the following diets\* useful.

## 4000 CALORIE LIQUID DIET

*Suggested Hourly Feeding*

- |         |                                     |
|---------|-------------------------------------|
| 7 A.M.  | Cereal gruel—1 serving (see recipe) |
|         | Milk—1 glass                        |
| 8 A.M.  | Eggnog—1 glass (see recipe)         |
| 9 A.M.  | Eggnog—1 glass                      |
| 10 A.M. | Ice cream                           |
|         | Fruit juice with egg (see recipe)   |
| 11 A.M. | Eggnog—1 glass                      |
| 12 noon | Cream soup—1 serving (see recipe)   |
|         | Milk—1 glass                        |
| 1 P.M.  | Eggnog—1 glass                      |
| 2 P.M.  | Ice cream—1 serving                 |
| 3 P.M.  | Eggnog—1 glass                      |
| 4 P.M.  | Ice cream—1 serving                 |
| 5 P.M.  | Cereal gruel—1 serving              |
| 6 P.M.  | Eggnog—1 glass                      |
| 7 P.M.  | Cream soup—1 serving                |
|         | Ice cream—1 serving                 |

\*These diets were worked out by Miss Jean M. Grant, dietitian, Nutritional Clinic, Hillman Hospital, Birmingham, Alabama.



8 P M Eggnog—1 glass

9 P M Eggnog—1 glass

*Note* Cup = standard 8-ounce measuring cup

Glass = 8-ounce water glass

*Approximate Food Value of Diet*

Protein	145 gm
Total calories	4134

### 4000 CALORIE LIQUID DIET

*Suggested Feedings Every Two Hours*

7 A M Fruit juice with egg—1 glass (see recipe)  
Cereal gruel—1 serving (see recipe)

9 A M Eggnog—1 glass (see recipe)  
Ice cream—1 serving

11 A M Eggnog—1 glass  
Milk—1 glass

1 P M Cream soup—1 serving (see recipe)  
Eggnog—1 glass  
Ice cream—1 serving

3 P M Eggnog—1 glass  
Milk—1 glass

5 P M Eggnog—1 glass  
Ice cream—1 serving

7 P M Cream soup—1 serving  
Ice cream—1 serving  
Eggnog—1 glass

9 P M Cereal gruel—1 serving  
Eggnog—1 glass

11 P M Eggnog—1 glass

*Note* Cup = standard 8-ounce measuring cup

Glass = 8-ounce water glass

*Approximate Food Value of Diet*

Protein	145 gm
Total calories	4134

### 4000 CALORIE "SOFT-SOLID" DIET

*Suggested Meals*

Breakfast, 8 A.M. Fruit juice—1 glass  
Cooked cereal—1 serving ( $\frac{1}{2}$  cup)  
Cream— $\frac{1}{4}$  cup  
Sugar—2 teaspoons  
Soft cooked eggs—2  
Milk toast—Toast, 1 slice  
Milk,  $\frac{1}{2}$  cup  
Butter, 1 square (2 teaspoons)  
Milk—1 glass  
Coffee—if desired

10 A.M.	Eggnog—1 glass (see recipe) Ice cream or puddings—1 serving
Lunch, 12 noon	Cream soup—1 serving (see recipe) Soft cooked eggs—2 Milk toast—Bread, 1 slice Milk, 1 cup Butter 2 teaspoons Mashed potato or boiled rice—1 serving ( $\frac{1}{2}$ cup) Butter—1 pat (2 teaspoons) Ice cream or pudding—1 serving Milk—1 glass
2 P.M.	Eggnog—1 glass
4 P.M.	Eggnog—1 glass
Supper, 6 P.M.	Cream soup—1 serving Cooked cereal— $\frac{1}{2}$ cup Cream— $\frac{1}{4}$ cup Sugar—2 teaspoons Soft cooked eggs—2 Ice cream or pudding—1 serving Milk—1 glass
8 P.M.	Eggnog—1 glass
<i>Note</i> Cup = standard 8-ounce measuring cup Glass = 8-ounce water glass	

*Approximate Food Value of Diet*

Proteins	147 gm.
Total calories	4153

4000 CALORIE "SOLID" DIET

*Suggested Meals and Between Meal Feedings*

Breakfast, 8 A.M.	Fruit juice—1 glass Cereal—large serving Eggs—2 Bacon or ham—if desired Toast—2 slices Butter—2 pats Cream— $\frac{1}{4}$ cup (for cereal and coffee) Milk—1 glass Coffee—if desired
10 A.M.	Eggnog—1 glass (see recipe)
Dinner	Lean meat, chicken or fish—3 ounces Potato macaroni spaghetti noodles, or dried beans or peas (1 serving) Vegetable—large serving (green or yellow vegetable—may be cooked or used as salad. If cooked add 1 square of butter. If used as salad, add 1 tablespoon mayonnaise) Bread—2 slices Butter—2 pats Dessert—1 serving Milk—1 glass

2 P M	Eggnog—1 glass
4 P M	Eggnog—1 glass
Supper, 6 P.M.	Lean meat, chicken or fish—3 ounces Potato, macaroni, spaghetti, noodles, or dried beans or peas (1 serving) Vegetable—large serving (green or yellow vegetable—may be cooked or used as salad If cooked, add 1 square of butter If used as salad, add 1 tablespoon mayonnaise) Bread—2 slices Butter—2 pats Dessert—1 serving Milk—1 glass
8 P.M	Eggnog—1 glass

*Approximate Food Value of Diet*

Protein	148 gm
Total calories	3980

RECIPES

<i>Eggnog</i>	6 eggs, 4 tablespoons sugar, 6 cups milk Beat eggs Add sugar Add milk Beat mixture well Chocolate syrup or vanilla may be added if desired <i>Makes 4 servings</i>
<i>Cereal Gruel</i>	$\frac{1}{2}$ cup of any kind of cooked cereal thinned to desired consistency with milk and served with $\frac{1}{4}$ cup of cream and with sugar if desired
<i>Cream Soup</i>	$\frac{1}{4}$ cup strained vegetable or canned tomato, pea, spinach or asparagus soup Add $\frac{1}{2}$ cup cream
<i>Fruit Juice with Egg</i>	Beat 1 egg well Add 1 cup fruit juice Add sugar as desired

It should be pointed out, however, that in certain diseases, such as allergy, diabetes and gastric ulcer, which necessitate restricting the kind or amount of food, these diets would not be suitable Such cases require individual diet therapy, a detailed discussion of which is beyond the limits of this paper

Important as food is in the treatment of nutritive failure, therapy should not be restricted to food alone Deprivation of nutrients usually has existed for years, and the average patient cannot eat enough food to supply the amount of these nutrients necessary to restore his health Accordingly, supplements of the nutrients in which the diet is deficient are given Until synthetic vitamins become available, dried brewers' yeast powder, wheat germ, liver concentrates and citrus fruit were given in treating deficiencies of the water-soluble vitamins As valuable as these substances were, and still are, there are times when synthetic substances are life-saving

It has been our experience that severe deficiencies of the water-

soluble vitamins are much more common than those of the fat-soluble group (A and D). Moreover, although symptoms of one deficiency may predominate, other deficiencies are almost certain to exist. Accordingly, in treating the clinical syndromes of *beriberi*, *pellagra*, *riboflavin deficiency* and *scurvy*, a basic formula is prescribed once to three times daily which contains 10 mg of thiamine, 50 mg niacinamide, 5 mg riboflavin, and 75 mg ascorbic acid. When the symptoms of one deficiency predominate, as they usually do, more of the vitamins specific for the predominating deficiency is added to the basic formula. In the case of *beriberi*, 10 mg thiamine is added daily, in *riboflavin deficiency* 5 mg riboflavin twice a day, in *scurvy* 100 mg ascorbic acid three times a day, and in mild *pellagra* 50 mg niacinamide three times a day. If the *pellagra* is severe, the patient is given 150 mg of niacinamide daily in addition to the basic formula. In most cases oral administration of vitamins is the method of choice, but if the patient is moribund, it may be necessary to give them by the parenteral route. When large amounts of *d*-glucose are injected daily, the inclusion of 20 mg of niacinamide, 5 mg of riboflavin, and 5 mg of thiamine is recommended. In a few instances of severe vitamin C deficiency, we have injected 500 mg of ascorbic acid in isotonic solution of sodium chloride.

Dried brewers' yeast powder, liver extract, wheat germ and rice polishings are excellent therapeutic agents in the treatment of *B complex deficiencies*. In addition to supplying all the known factors of the B complex and probably some as yet unknown, they contain significant amounts of protein and other essential nutrients. The amount of these materials administered depends upon the severity of the disease. We usually give daily from 4 to 6 ounces of dried brewers' yeast powder or oral liver extract, from three to four doses of 20 cc of parenteral liver extract, or from 150 to 300 gm of wheat germ. The flavor of these materials, which some patients find so disagreeable that they will take them only under protest, can be masked somewhat by combining them with milk or tomato juice or by mixing them with water and adding tomato catsup.

In *vitamin A deficiency*, the diet of the adult is supplemented with 50,000 units of vitamin A daily for at least two months. The clinical response to vitamin A deficiency is slow, and it may be necessary to continue treatment over a long period of time.

In treating persons debilitated solely by nutritive failure, we do not regard treatment as satisfactory until the patient has gained in strength, until his weight has returned to normal, and until he is able to return to work and to continue to work regularly.

Following the application of these methods of diagnosis and therapy we have seen several hundred persons with nutritive failure completely rehabilitated. Prior to treatment many of them had been unable to work for years and were entirely dependent upon their families or

upon social agencies. They are now contributing their efforts in various fields of production. The type of work in which 800 persons who were debilitated solely by nutritional deficiencies are now engaged is illustrated in the following table:

Armed Forces	41
Agriculture	101
Domestic service	359
Industry	299

The 800 persons in this group, as do most of the patients in our clinic, developed nutritive failure solely as the result of an inadequate food intake. We have treated many patients, however, in whom nutritive failure was secondary to organic disease and a few whose chronic addiction to alcohol has led them to substitute alcohol for food. When organic disease or addiction to alcohol is the predisposing cause of a nutritive breakdown, rehabilitation is much more difficult than when an inadequate food intake is the sole cause. In some cases it is impossible. Nevertheless, many of these persons can be rehabilitated and the health of others can be improved to such an extent that they can lead more comfortable and useful lives than they did prior to treatment. In persons with deficiency diseases that are secondary to organic disease, this can best be accomplished by combining nutritive therapy and treatment of the disease that predisposed to nutritive failure. Successful treatment of the patient chronically addicted to alcohol is based on adequate nutritive therapy, education of the patient in regard to the importance of eating an adequate diet at all times, and continued observation of the patient so that therapy can be instituted immediately should any symptoms of nutritive failure reappear.

I wish to stress that our work in the field of rehabilitation has been concerned wholly with making it possible for the man to perform work. We have made no attempt to fit the man to the job nor the job to the man. We have given no physical training nor have we used any tests for scoring performance. Our only concern has been in restoring the patient's nutritional status and health.

#### SUMMARY

Few physicians realize the meticulous clinical study needed before a diagnosis of deficiency disease is justified. The science of nutrition has advanced so rapidly that the practicing physician naturally wonders what he can include as valid in his day-to-day practice of medicine. By the application of the methods of diagnosis and therapy described in this paper we feel certain that he will be gratified by seeing many patients fully recover their health and return to work.

Proper nutritive therapy throughout the acute stage of illness and convalescence completely rehabilitates many persons debilitated by



- 8 Schultz, A S, Atkin, L and Frey, C N Determination of Vitamin B<sub>1</sub> by Yeast Fermentation Method Indust. & Engineer Chem (Analyt. Ed), *14* 35 (Jan ) 1942
- 9 Vilter, S P., Spies, Tom D and Mathews, A P A Method for the Determination of Nicotinic Acid, Nicotinamide and Possibly Other Pyridine-Like Substances in Human Urine J Biol Chem., *125* 85-98 (Sept ) 1938
- 10 Snell, E E, Strong, F M and Peterson, W H A Microbiological Assay for Riboflavin Indust & Engineer Chem (Analyt Ed ), *11* 346 (June) 1939
- 11 Spies, T D., Stanbery, S R., Williams, R. J, Jukes, T H and Babcock, S H Pantothenic Acid in Human Nutrition J.A.M.A., *115* 523-524 (Aug 17) 1940

# THE PROBLEM OF REHABILITATION IN CIVILIAN MEDICAL PRACTICE

WILLIAM BENJAMIN SNOW, M D \*

## DEFINITION AND AIMS

THE word "rehabilitation" has many applications. In these wearisome war years minds turn to postwar rehabilitation with reference to national and political changes worldwide in scope, social changes predicated on rebuilding a desolated world, economists plans for rehabilitation of finances, and policies formulated for a better world based upon the greatest number of "freedoms" possible consistent with maintenance of law, order and future happiness as far into the future as our imagination can extend.

We hope for all of these, and better minds than medical ones can shape such destinies. The medical profession and allied agencies are faced today with certain problems which the war has brought immediately into focus. Many in the medical profession are suddenly realizing that a new field of usefulness has opened up, namely the rehabilitation of handicapped individuals. Processes of rehabilitation are being discussed and furthered as never before. More minds devoted to the problem should probably bring more complete and satisfactory results. On the other hand, war and its associated emotional outpourings bring with them a tremendous amount of loose, careless thinking which avails little of real usefulness. There have been some new problems in rehabilitation which have come out of this war, but the greatest amount of rehabilitation needs are not new, nor are they peculiar to war. Processes of rehabilitation are a constant need wherever men work, play and live in and about the complications of machine-operated society.

"Rehabilitation is the restoration of the handicapped to the fullest physical, mental, social, vocational and economic usefulness of which they are capable."<sup>1</sup> Unfortunately, the aims of this utopian definition exceed the accomplishment fulfilled in the lives of a large percentage of normal individuals. At any one moment in any individual's lifetime he represents a very complicated collection of experiences, impressions, emotions, aims and ambitions. He enjoys a degree of health dependent on his hereditary endowments, health habits, education, experiences and the physical impressions of past illness. Psychically he can be identified in one or more groupings, as phlegmatic hyper-

---

Director of Physical and Occupational Therapy Columbia Presbyterian Medical Center Associate in Medicine, College of Physicians and Surgeons, Columbia University New York City



tensive, calloused or sensitive, emotionally stable or unstable, kind or unkind, generous or greedy, slothful or alive, ambitious or lacking in incentive, to mention a few. With these thoughts in mind, rehabilitation of an individual who has been dislocated from the normal trend of his life through ill health, disease or injury, must be considered as no simple problem. As physicians, we are interested in physical and mental restoration of this individual. His problem is the problem of rehabilitating John Jones, a man, with a past and a future different from that of any other individual in the world.

Actually, many individuals in civilian life who are subjects for rehabilitation never did amount to very much. When we try to fit the utopian definition of rehabilitation to these figures we attempt an impossibility. On the other hand, the fact that an individual has not made the most of his opportunities does not mean that he may not be shocked from indifference into sober reality, and that his disability may become his saving grace and represent the first move toward his taking a useful place in society.

The psychology underlying rehabilitation of the handicapped represents the crux to the problem. Unless a proper psychological reaction is obtainable, rehabilitation cannot proceed. Those concerned with rehabilitation must represent a united front which goes to work on the subject with tact, judgment, understanding and patience all combined in such a manner as to preserve the dignity and self-respect of the individual being rehabilitated. This is America. As such our medical applications are best when carried out democratically.

#### THE REHABILITATION PROBLEM IN A CIVILIAN HOSPITAL OR MEDICAL CENTER

It Differs from the Military Problem of Rehabilitation.—I would like to discuss certain thoughts covering rehabilitation in a hospital or medical center. The thoughts will not be directed toward war injuries for the reasons already set down. Likewise, the rehabilitation program which has to be met in civilian life is far more complicated. It includes many classes of individuals and medical conditions which by their very nature never would be found in a military set-up. Hereditary handicaps, certain childhood diseases and orthopedic deformities are a few of these. Likewise, the doctor-patient relationships in the armed forces and in civilian life digress widely. Certain compulsions exist in military medicine which are nonexistent in civilian practice. Free choice of physician by the patient and the normal competition existing in civilian hospitals and private practice likewise affect rehabilitation. Possibility for independent action in treatment free from official directive, makes for the more independent handling of rehabilitation in civilian practice than is possible in the Army. In the latter, exigencies may demand invocation of certain decisions which mitigate against the individual in a system where "the greatest good for the greatest number" and "fighting manpower" are the immediate aims of rehabilitation. The

further back from the front lines the patient gets, the nearer will these two attitudes in rehabilitation converge

**Peace Will Bring Changes**—In the postwar period, many veterans with disabilities will seek medical assistance in other than government hospitals for several reasons. Physicians who have been exposed to the problems of rehabilitation will return with advanced ideas on rehabilitation and seek an outlet for these ideas in the civilian hospitals to which they will return. Thus awakened medical interest in rehabilitation will require the introduction of considerable changes in hospital practice. Civilian hospitals should investigate the problem of rehabilitation before it is forced upon them too late. The trend is already here.

**Convalescent Care—a Weak Link**—Rehabilitation is only a step removed from convalescence. Convalescent care is probably the weakest link in the chain of medical service. Rehabilitation begins with the making of a diagnosis. Convalescence follows after the first steps of treatment have been taken. Every patient put to bed will either convalesce and be rehabilitated, become chronically debilitated, or die. When the diagnosis is established and the gravity of the patient's condition is weighed, the physician has the right to an opinion as to what the ultimate outcome may be. If the patient's prognosis is hopeless, certain obligations exist. If the condition is to become chronic, some idea certainly exists in the physician's mind as to what is the best long-range program to pursue to extend the patient's life with the greatest degree of comfort, happiness, independence and freedom from handicap.

If the diagnosis is suggestive of recovery to somewhat the patient's original state, depending on the illness and its expected duration, certain prophylactic, curative and convalescent procedures will be indicated.

**The Harmful Effects of Prolonged Bed Rest**—Prolonged bed rest, if required in the treatment of an illness, carries with it certain physiologic alterations associated with inactivity.<sup>2</sup> Medical men have been fully aware of these tendencies but in a vast number of instances we have done nothing about it. For years we have hurried old folks out of bed to prevent circulatory stasis and muscular atrophy from occurring, and have permitted younger persons to be victims of the same complications. There is a distinct progressive upsurge in cutting down bed rest today. Internal fixation in orthopedic and fracture practice is shortening convalescence and lessening debility in these fields. Surgeons are getting patients out of bed much earlier after certain procedures, and new procedures are being advocated particularly because time of bed confinement is reduced by their use.

**A Program for the Patient Destined for a Prolonged Hospital Stay**—Of necessity, many medical and surgical patients must remain in bed for a considerable length of time. Very often the physician's interest, very acute during the period of diagnosis, surgery or early treatment of a

given case, lags with the eager anticipation of other newer, more interesting diagnostic or treatment problems. The interesting case of yesterday becomes the forgotten indifferently treated patient of today. Patients whose convalescence is prolonged have many hours for reflection. Unfortunately some cannot lift themselves by their boot straps. They lapse physically and mentally into a desultory static phase for no other reason than that nothing is being done for them. These patients not only need physical rehabilitation but often psychic stimulation as well.

The patients who are doomed to chronicity are the next problem to be considered. These cases represent what is probably one of the greatest needs in medicine today. How can this large group of patients best be cared for? The total recovery possible in a given case will depend on the plan for convalescence which his physician chooses. Detail during convalescence will have much to do with determining the extent of ultimate incapacity.

One of these details is the application of *therapeutic exercise* during the illness proper or during convalescence where specific indications exist for its use. Exercises are utilized in rehabilitation in the following classifications:

1 *Exercises to enhance tissue drainage and improve circulation*. In convalescence and rehabilitation such applications are elevation and depression exercises of the extremities instituted before active ambulation is started. The dangling of legs several times daily prior to ambulation builds up circulatory tonicity prior to adding the load of walking attempts to the patient's routine. Massage and periods of elevation of the extremities are given in conjunction with such exercises if the tendency to edema after dependency is too marked.

2 *Exercises to improve range of joint function* through relaxation of muscle spasm, or stretching of tissues and freeing of adhesions. Such routines are useful in the care of arthritics who have been long immobilized, burn cases, orthopedic and traumatic cases, and hemiplegics. Hemiplegic patients are one of the most neglected types of patients seen in practice today. The physician treats the patient following the acute etiological incident, and when stabilization occurs he too often leaves him to find his own way through ambulation. These patients should be treated early with passive motion of all joints to avoid restriction of joint movement in the presence of spasticity. Splints likewise may be helpful. Gentle stroking massage and muscle reeducation should be given throughout the course of the illness. Too often, though the pathologic involvement is lessened centrally, these patients are not taught to pick up function at the periphery. Close observation of the cause of incoordination in each case should be made and efforts made to smooth out function through reestablishment of lost patterns of function by strict disciplinary muscle reeducation. There would be far less resultant disability in this group under such a routine.

Arthritics<sup>3</sup> with prolonged swellings, especially rheumatoid arthritic patients in whom sedimentation rate remains elevated, must begin ambulation with extreme care. Often the smallest amount of exercise is injudicious. Splinting against deformity, heat therapy, and simple nonweight-bearing bed exercises may be all that can be carried out for a considerable time. Often attitudes of flexion deformity are not actually due to contracted muscles but rather to weaknesses in extensor groups. Discrimination is necessary here. Maintenance of muscle balance is important in the ambulation of these cases. Other types of exercises also apply to this group.

3 *Exercises to improve muscle power* These exercises are admissible in any convalescent patient, and in certain pathologic processes are the most important element in the patient's rehabilitation. Early considerations as to power requirement in muscles essential to ambulation must be made. Much loss of time during later hospital stay will be saved if proper exercises are instituted early. Patients who will use crutches need triceps muscles and scapula fixators and a hand grip. Patients who will walk with leg disabilities need to have the abdominals strengthened. Trapezes over beds are of great help in assisting patients to move themselves about, but they also overdevelop flexor muscles at the expense of extensors. The extensors always suffer in bedfast patients. It takes time to develop muscle power. Muscles can only develop through active volitional use of the muscles to be strengthened. The effort must be stepped up and fatigue avoided if consistent progress is to be made. This developmental type of exercise is indicated in such diseases as myelitis, especially the infectious myelitides including poliomyelitis, and in orthopedic and traumatic cases.

4 *Exercises to preserve function and preclude atrophy* have been dealt with elsewhere in this paper.

5 *Exercises to improve coordination* are extremely important in neurologic syndromes of central and cord origin. They are likewise important in teaching walking technique following disability. Walking exercises are those for coordination and also for building up muscle power. They must start with simple balancing with attention directed toward how weight is shifted in locomotion; then steps are taken, then with increased power the base of the step is narrowed and measured distances for walking are gradually added. When possible, coordination in walking is best started in weak patients with the greater part of the body immersed in water.

While discussing coordination exercise, it is important that occupational therapy be brought into the picture. As soon as a patient has two joints in function, in the rehabilitation of an injured member, coordination is possible. The coordinated efforts directed toward some definite incentives as are found in occupational therapy are considerably more acceptable to the average patient than are exercise routines.

per se Functional use of occupational therapy to improve facility in movement represents one of our most useful therapeutic agencies

6 *Exercises to step up metabolism* are indicated in those cases in which obesity becomes a complication For example, in orthopedic and arthritic cases, bearing of excessive weight interferes with mechanics of locomotion, or aggravates an inflammatory condition The institution of such exercises in asthenic patients may be the first step toward making them feel alive Such metabolic exercises must ultimately be quite vigorous if they are to be effective Hence, they can only be adapted to cases in which cardiac disability is not a factor Deep breathing exercises likewise improve circulation and increase vital capacity in such patients

7 *Exercises for postural improvement* are indicated in the convalescence of many patients Proper distribution of gravity in posture will hasten convalescence Weak, tired patients are apt to assume postures of relaxation Such attitudes may become habitual if no attention is paid to them Continuation of poor posture often results in development of structural pains due to poor body mechanics These exercises are a combination of muscle strengthening, coordination, balance and rhythm

*The Need for a Convalescent Ward, and for Intramural Hospitalization*  
—There comes a time in the illness of patients when it is no longer appropriate or necessary for them to remain in the hospital They have become totally dependent on hospital service The burden of them appears such that it is frightening to their families It may be weeks or months before they will be mentally and physically able to return to anything approaching the routine of life to which they were previously accustomed Social service or friends cannot provide for their needs Their deficiency is within themselves Many have only sufficient strength or concentration to carry on alone for but a brief part of each day Many have residual disabilities, or routines for recovery which require skilled assistance or nursing care Many require special services, as physical and occupational therapy, which cannot conveniently be brought into their homes or which cannot be provided in a convalescent home Patients presenting such subacute or chronic needs for physical restoration may require months to prepare themselves to cope with the daily routine of living and to take their places in society Some never will be able to do so I particularly have in mind the rheumatic and arthritic group, those with progressive lesions of the central nervous system, the hemiplegics, and patients with advanced peripheral vascular disease, chronic osteomyelitis and surgical tuberculosis Necessary treatment is expensive, time-consuming and definitely out of reach of all except the so-called "well-to-do" class of patients (the small minority) A great and growing need exists for institutions equipped to care for such temporarily or permanently invalided patients—institutions supported by private or public funds.

Some measure of security has been provided for the tuberculous, the neuropsychiatric, the blind, the cardiac, the crippled child, and the aged and infirm patient.

In the care of the convalescent patient needing an extended hospital stay, much could be done to expedite his exodus from the hospital and something should be done to make less urgent his discharge from the hospital before he is able to carry on by himself. Two definite needs present, a need for a convalescent ward, and a need for intramural hospitalization.

Many patients admitted to general hospitals with immediate needs for medical and surgical care ultimately have need for extended hospitalization. It is not considered safe to transfer many such patients to convalescent facilities even though such arrangements might contribute much that is psychically and physically advantageous to convalescence. In these patients, the major needs of treatment have been met, convalescence is definitely established, but it is advisable that the patients be kept under observation by the doctor or the service who have followed them through their illnesses. A certain amount of treatment still is imperative and some types of ambulation must be carefully controlled while the patients are being rehabilitated. There is still a possibility of sudden retardation of restoration due to unpredictable but not unusual sequences or complications common to patients with their particular ailment, or which may follow the procedure to which they have been subjected. We cannot remove these patients from our direct supervision. Yet they occupy beds on active medical and surgical services, precluding the admission of more acute needy cases. On teaching services they slow up the admission of good teaching case material. Such patients are found in all divisions of a general hospital. A few examples are the postpneumonia and postcardiac patients, rheumatic and arthritic patients,<sup>3</sup> patients with certain types of myelitis, certain fracture patients late in their treatment, orthopedic patients for whom rest and physical therapy rather than surgery are indicated, or who have been subjected to surgery but must be under observation, patients who have had cerebral accidents, and a host of others which must occur to us as we concentrate on this problem. All these patients probably need, among other things, some form of physical therapy or occupational therapy.<sup>4</sup>

There is a certain point in the care of these patients when we wish we could move them along. They are in wards with other patients much sicker than themselves. Rest is disturbed and surroundings are depressing. Psychologically they need more hopeful and stimulating surroundings. They need special care of a different type—rehabilitative—tonic—ambulatory. These needs are common to all. At this time their condition should be carefully weighed. Their treatment is probably stabilized and could be carried out with less particular attention previously necessary. On the other hand, the physical recen-

which they require could be much better handled were they grouped together in one place. If months of such care are indicated, we have one problem, if weeks only are necessary, it is quite another. Those requiring a reasonably short stay might be cared for in a rehabilitation ward. This ward might best be under the direction of the one in charge of Physical Medicine, as all such patients will require those facilities, and the personnel in Physical Medicine are best equipped technically to work with these patients. The nurse in charge of such a ward should not only be trained in nursing but also physical therapy and rehabilitation. Such a ward should be provided with adequate space for special exercise treatment, equipment for resistive exercises, underwater exercise facilities, ample supplies of crutches, canes, walkers, and other essential equipment.

These needs are being met at present in a most disadvantageous way in most institutions. Much time is lost in transporting patients and equipment, often long distances. There is a lack of uniform direction in plan of treatment because often the physician who is brilliant in giving the care in earlier stages of the illness is quite ignorant of the psychology and technical procedures required for rehabilitation. A rehabilitation ward working in close cooperation with the physicians most interested in these cases would make for economy of time and personnel. An improved psychology would exist in the patient who would feel that he is progressing in the right direction. He would be sharing similar problems with his co-patients in the ward. This would unquestionably accelerate his movement toward home and ultimately send him home less of a burden to himself and his family.

There is need for such a facility to care for *poliomyelitis* patients if they are to be admitted to a hospital in any number. There is a growing appreciation in contagious disease hospitals that such institutions are not geared to the treatment of poliomyelitis. The need for isolation is now considered less than is the need for early treatment. General hospitals are planning to accept these cases under routine precautions. There is no early treatment for poliomyelitis<sup>5</sup> except symptomatic care to preserve life, relieve pain and conserve energy. Later, treatment is indicated to bring maximum comfort to the suffering patient, prevent possible deformity, increase flexibility, and then guide the patient through a period of muscle training, coordination and ambulation. The care the first two weeks will consist of neurologic and pediatric treatment, nursing and some physical therapy. After two weeks the case becomes primarily a problem of physical medicine and orthopedic consultation. These patients fit well into the class of patient who should not be in general wards, but in a rehabilitation ward under direct supervision of Physical Medicine.

What is to be done with those patients whose rehabilitation is to be long extended? Unfortunately, hospitals for chronic diseases are rela-

tively few and widely scattered. Many of these patients have a good prognosis for ultimately resuming a normal existence. Removal to another hospital would not be the best plan. Much better care and follow-up could be carried out by the staff which has carried them over the hump of their illness. Though the further counsel of numerous physicians may be required, it seems uneconomical to spend time re-orienting an entirely new staff to the patient's particular needs, with the hazard of conflicting medical opinions. Convalescent homes are not the answer even if directly associated with a hospital. Such abodes should be set up and operated as interim resting places where no treatment is required during the patient's convalescence.

The requirement is for an intramural convalescent rehabilitation hospital, preferably physically adjacent to the hospital where early care has been given. Admission to this hospital might be limited to patients whose prognosis for ambulation and self-care on admission is good. All these patients should be able to walk out of the door when discharged. Incurable patients should be barred from admission. The facilities should be sufficient to provide not only special rehabilitative procedures but also any postsurgical and medical needs as remain necessary during convalescence. Physical Medicine will hold an important position in this medical institution.

This specialized hospital being adjacent to the general hospital will have available any and all consultants to meet special problems. Records will be easily available for follow-up comparisons, and should new emergencies arise, transfer back to the original hospital would present no problem. Progressive rehabilitation, especially in orthopedic and plastic cases, could be continuously carried forward with the patient retaining maximum of function between a series of operative procedures. Ample and diverse facilities for recreation and physical exercise indoors and outdoors should be available to these patients as the physical bans are lifted with progress of convalescence. It might well be that the occupational activities of patients at this stage be guided into prevocational channels.

**Rehabilitation and Reconditioning**—In the armed forces we are seeing two different classifications set up. Rehabilitation and Reconditioning. In the final analysis, rehabilitation probably accents special medical procedures necessary to mental and physical restoration. Reconditioning has two places in a patient's illness. Early in his illness, reconditioning is used for the prevention of loss of vitality to which a patient, however ill, may be subject. Later in the soldier's illness, after physical inhibitions are reduced, he is placed in a reconditioning program to provide physical activities which build up his strength at an accelerated rate, progressing toward fitting him for return to full active duty. Reconditioning programs are under medical supervision and include recreation as well as direct group exercises. The armed forces have



taken advantage of the special knowledge of those trained in Physical Education to assist with reconditioning Occupational therapists are also included in the reconditioning set-up

This grouping in the program of reconditioning works out satisfactorily, and in wartime such is the outstanding requirement, however, it leaves much for improvement Physical therapy has been placed under Orthopedics in the Army organization There are certain doubts as to the soundness of such an arrangement One conversant with the broader concept of physical therapy and its close tie to occupational therapy in treatment must wonder whether it might not be awkward to facilitate the use of physical therapy in neurology, psychiatry, plastic and general surgery, under such a plan

**The Place of Physical Medicine in the Hospital Organization**—Physical medicine will some day probably assume a position of more major importance in the hospital organization plan It will be set up as a department self-sufficient to service all the treatment and rehabilitative needs which can only be made available through the specialized equipment, education and skilled technics acquired by personnel trained in physical medicine, i e., doctors, physical and occupational therapists, special orthopedic nurses, and recreationists Education in physical medicine is being stimulated by this war, and programs are developing in various medical centers<sup>6</sup> directed toward basic research supporting procedures in physical medicine, and toward making available accumulated knowledge in the field of physical medicine

Physical therapy can be of great value in *prophylaxis* A routine of massage to the lower extremities in acute cardiacs, pneumonia patients, and postoperatively to hernia cases, can be very helpful in preventing the occurrence of circulatory complications Routines of exercises for bedfast patients who are not generally ill, but whose incapacity is limited to a localized condition in one or two extremities, will do much to maintain efficient circulation, lessen lowered resistance and prevent atrophy due to disuse Such patients will be in better condition when the time for ambulation arrives The organization of such a routine throughout an institution requires careful planning so as not to interfere with purely medical routines

**Earlier Ambulation of Patients Is Indicated**—A scheme for earlier ambulation of patients in hospitals should be worked out The Army Air Forces have done a fine piece of work and have proved definitely that virus pneumonia patients do best when at a certain time in their resolution they are rather rapidly and progressively ambulated At just what moment it is expedient to ambulate patients of all kinds will require careful consideration There can be no doubt that our physiology normally follows the general rule of "supply and demand," and we have learned the hard way that perhaps these demands should be created earlier Note, in this respect, osteoporosis due to disuse and the improvement in bone healing with weight-bearing, the response of func-

tional hearts to exercise, the rapid improvement in function and reduction in periarthritic disabilities with judicious activity, the need for constantly progressive effort in treating weak muscles, the moderated activity in treatment of peripheral vascular cases, and many other such examples

**Problems of the Patient about to Be Discharged**—There is another gap in treatment needing exploration. Certain patients are discharged from the hospital who, after partial rehabilitation has been carried out, can safely be returned to their own particular environment. Before they can be discharged, consideration must be given to the sort of environment to which they are returning. Is the patient male or female, married or single, child or adult, or aged? Is he or she returning to a home, with all that word implies, to a furnished room, or to some other domicile? Is he entirely capable of self-help, or in need of physical assistance? Will he need treatment? If so, how often? Will it be possible for him to return to the out-patient clinic or doctor's office? If so, will he need transportation, or is his home so far away that such visits would be too time-consuming or require too much effort to be practicable? Is the patient intelligent enough to be entrusted with home routines? These are just a few of the considerations of this moment.

The social service workers can be very helpful in ascertaining the answers to many of these questions. Many outside agencies exist, such as visiting nurse groups, crippled children's programs and associations, the Red Cross, and community workshops,<sup>7 8</sup> which may render assistance in special cases.

There is often an hiatus in care at this point. Treatment considered necessary the day prior to discharge of the patient is conveniently forgotten because we do not know how to organize its inclusion after discharge. This hiatus would be far less were the rehabilitation ward and intramural hospital in common existence and well integrated with the host of rehabilitative agencies at present available but far too little publicized. The problem boils down to education, publicity, utilization and integration.

#### FEDERAL, STATE AND INDUSTRY'S INTEREST IN REHABILITATION

The federal and state governments have been interested in rehabilitation for years. Programs for crippled children exist in most states, orthopedic programs in many. Large insurance companies have been forced to organize for rehabilitation of their insured.<sup>9</sup> Many would be anxious to cooperate with organized medicine in developing rehabilitation facilities. Insurance companies spend thousands of dollars annually in compensation fees, which expenses could be grossly curtailed if some of the existing laws governing compensation could be rationalized.<sup>10 11</sup> Free choice of physician is a democratic procedure but often leads to irregular practices and scandals, to ambulance chasing

and often the patient and the insurance companies are both victimized as a result

Industrial medicine cannot be passed over in discussing rehabilitation. Such programs have to do with maintenance of a high standard of health, improved working conditions, and also care for employees when ill or injured. The overall treatment of the industrial medicine problem is one intimately entangled with other problems such as pre-paid medical care, workmen's compensation,<sup>13</sup> rehabilitation,<sup>4</sup> and employment of the handicapped.<sup>11, 13, 14, 15</sup> Further consideration of industrial medicine cannot be included in this opus. Similarly, the problems of the returning veteran and the broad subject of vocational rehabilitation for the handicapped<sup>22</sup> are not subjects to be discussed under the title of this discourse. A few recent references are included herewith for those interested.<sup>16, 17, 18, 23</sup>

#### REHABILITATION IN THE HOME AND THE DOCTOR'S OFFICE

Up to this point I have largely concerned myself with hospital problems, that is, to patients admitted into the hospital. There is a large group of patients who require rehabilitation after leaving the hospital. Many other patients never are admitted to hospitals but are encountered in medical and surgical practice in the home or the doctor's office. Those treated in the home will be managed much as they would be handled in the hospital except that laboratory assistance and certain forms of treatment are more difficult to arrange. Most physicians develop means in their practice to meet these problems. Ambulation may suffer due to lack of available assistance. Each physician should make it his duty to acquaint himself with all special services available in his community upon which he may call to help him with home-bound patients. In his office practice he may have space and equipment for physical therapy. If so, he should have well trained assistants to give such treatment. Likewise, he should avoid the pitfall of using physical therapy promiscuously on his patients. Physical therapy should never be given to a patient unless a particular physiological response definitely beneficial to the patient can be anticipated. Consultation advice in rehabilitation should be sought when the physician feels insecure as to what his next step should be.

Rehabilitation of patients in rural areas is difficult due to time, distance, transportation problems and lack of concentration of facilities. Public health agencies, traveling clinics and orthopedic and state rehabilitation programs are all available to assist the physician and his patient. Federal funds<sup>10</sup> in equal amount to state expenditures assist in providing means for physical restoration. The integration of such a program is well demonstrated in the Ohio Plan.<sup>20</sup> The Peoria Plan<sup>21</sup> is an excellent example of what a local city in Illinois has worked out for care and placement of the handicapped. This plan as outlined is adaptable to smaller communities.

## REHABILITATION OF SPECIAL CLASSES OF PATIENTS

**The Mentally Ill**—Rehabilitation in relationship to the mentally ill patient has not been mentioned. Such considerations are not admissible as such in this paper. Psychiatry has pretty well grooved channels in this field. New methods of group treatment for war psychoses are being explored and found practicable. Many physically ill patients lapse into the group of mentally ill. Fewer of these lapses would occur were a live rehabilitation program available in the hospital setup. Functional neurologic conditions respond to well directed physical and occupational therapy procedures when closely integrated with proper psychologic treatment.

**Children with Cerebral Palsy**—A special group requiring rehabilitation are children with cerebral palsy. Much can be accomplished with these patients. It is imperative that they be discovered and their condition evaluated as early as possible. The location and degree of the pathologic involvement should be determined, also whether or not it is static or progressive. The patient's intelligence quotient should be determined, and we must include in our evaluation the extent that the intelligence quotient is influenced by lack of skill or speech deficiency on the part of the patient. Certain of these patients will require surgical assistance and orthopedic appliances. Close cooperation between neurologist, the specialist in physical medicine, and the orthopedic consultant will be necessary in planning the rehabilitative program of these patients. The children are young, their futures will be measured in terms of self-help, locomotion, and probable educability. The possibilities should not be overestimated. The preschool child should be directed toward maximal utilitarian function. The preschool child should be treated with physical therapy particularly if he is inco-ordinate, athetoid or choreic. Even if spastic, much can be done for him in these tender years and anticipated deformity can be lessened.

The problem of the child with cerebral palsy is a community problem. Here the slogan of the Army, "the greatest good for the greatest number," holds very well. The community owes each of these unfortunately affected children a chance for rehabilitation. Public and private funds are available and should be utilized to the fullest extent. Local departments of health and education should combine their efforts toward case finding and continuous treatment. Hospitals and schools should be brought together in treatment. Transportation problems should be studied and where possible a common denominator for transportation covering treatment and education should be estimated. Treatment should be entirely under medical supervision, and only by skilled technicians. Home teachers should be provided where necessary. The children's parents should be progressively educated to the problems surrounding these children and their cooperation maintained throughout the treatment period. Vocational <sup>and</sup> <sub>is</sub> brought into the picture at the proper moment. The entire

should be set up with the least amount of accent on each individual's personal handicap, consistent with individualization of his case. The hopeful end results are independent locomotion, complete self-care, a minimum of "cripple complex," and the hope of individual maintenance through vocational training.<sup>22</sup>

### CONCLUSIONS

The impressions set down in this short treatise may help to crystallize thinking on rehabilitation. The aims of rehabilitation and convalescence are to aid the patient toward regaining his physical strength and normal facility of movement, to rejuvenate the spirits of an individual and minimize any tendency to lasting disability following illness or injury.

It may be concluded that

1 Total rehabilitation requires the combined efforts of many individuals and agencies—medical, social, financial and others.

2 The use of agencies of physical medicine are imperative to any rehabilitation program.

3 There is need for definite factual consideration of many problems which present themselves during rehabilitation and convalescence.

4 Changes in plant and administration will be necessary if rehabilitation is to be carried out effectively and efficiently in the modern hospital.

5 There is need for the development of a new type of convalescent hospital.

6 There is need for informative publicity both to the public and the medical profession as to services available to assist in rehabilitation.

### BIBLIOGRAPHY

- 1 Definition adopted by the National Council on Rehabilitation, 1790 Broadway, New York City, August, 1943.
- 2 Dock, William. The Use and Abuse of Bed Rest, from Conferences on Therapy. *New York State J. Med.*, 1944, pp. 724-730.
- 3 Snow, W. B. The Relation of Physical Therapy to Arthritis. *New England J. Med.*, 229:959-965 (Dec. 23) 1943.
- 4 Snow, W. B. Practical Application of Physical Therapy in Rehabilitation. *Arch. Phys. Med.*, Vol. 26. In proof.
- 5 Snow, W. B. The Treatment of Poliomyelitis. *J. Pediat.*, 25(1): 17-24 (July) 1944.
- 6 War and Post-War Rehabilitation and Reconditioning. Bulletin of Information, Baruch Committee on Physical Medicine, December, 1944.
- 7 Zeiter, W. J., Gamble, Shelby and Grete, Bell. A Comprehensive Rehabilitation Center. *Arch. Phys. Ther.*, 25(11): Nov., 1944.
- 8 Thumbs Up. Institute for Crippled and Disabled, 400 First Avenue, New York.
- 9 Aitken, Alexander P. Rehabilitation of the Industrial Casualty. *Arch. Phys. Med.*, 26(1): Jan., 1945.
- 10 Report, Committee on Compensation. National Council on Rehabilitation, April 5, 1944.

- 11 Employment of Physically Handicapped, with Bibliography Liberty Mutual Insurance Company Boston
- 12 The Employment of Disabled War Veterans and Other Disabled Persons Association of Casualty and Surety Executives, 60 John Street, New York 7, New York
- 13 O'Connor English Fifteen Years Experience with Handicapped Employees Executives Vol 22, No 10, Metropolitan Life Insurance Company Oct., 1944
- 14 Breech, Ernest R Successful Experience with Handicapped Workers. Executives Vol 21 No 11 Metropolitan Life Insurance Company 1943
- 15 Editorial Employment of Physically Handicapped New York State J Med, March 15 1944
- 16 The Employment of the Handicapped Veteran. Metropolitan Life Insurance Company New York City
- 17 War Veterans Reinstatement Plan. R 1100 A Westinghouse Electric and Manufacturing Company
- 18 Rehabilitation of the Disabled Serviceman—a Selected Bibliography Bull Russell Sage Foundation Library No 162 Nov., 1944 Russell Sage Foundation, 130 East 22 Street, New York 10 New York
- 19 Regulations Governing the Plans and Programs of Vocational Rehabilitation Pursuant to Public Law 113, 78th Congress, Part 6, p 11 issued by Office of Vocational Rehabilitation Washington, D C., Oct. 9 1943
- 20 The Ohio Plan for the Administration of Vocational Rehabilitation for Disabled People in Ohio Bureau of Vocational Rehabilitation Columbus, Ohio p 18
- 21 The Peoria Plan 415 Liberty Street, Peoria 2 Illinois.
- 22 Deaver George G and Brown, Mary Eleanor Physical Demands of Daily Life Institute for Crippled and Disabled New York City, 1945
- 23 Aid to the Physically Handicapped Parts 1-8 Hearings before the Committee on Labor Subcommittee to Investigate Aid to the Physically Handicapped 78th Congress, August through December 1944

## CUMULATIVE INDEX

- ABORTION, early, progesterone in, *Jan*, 264
- Achlorhydria, acid therapy, *March*, 426
- Actinomycosis, *March*, 338
- Addison's disease, desoxycorticosterone acetate in, *March*, 435
- Adenoma, parathyroid, *March*, 390-393
- Agglutination test for brucellosis, *March*, 353
- Albumin, human, *March*, 433
- Albuminocytologic dissociation in acute infectious radiculoneuritis, *Jan*, 1
- Alcohol injections for facial pain, *Jan*, 77
- Alcoholism, criminal responsibility and, *Jan*, 212
- Alloxan in production of diabetes, *March*, 436
- Aluminum hydroxide in hypoparathyroidism, *March*, 435
- powder in silicosis, *March*, 437
- Amenorrhea, hormone therapy, *Jan*, 258, 260, 263
- Amigen, *March*, 433
- Amino acids, parenteral use, *March*, 433
- Androgen therapy, advances in, *March*, 436
- in menstrual disorders, *Jan*, 265
- Anemia, hemolytic, acute acquired, *May*, 695
- Lederer's, *May*, 702
- pernicious, *Jan*, 229
- clinical types, *Jan*, 230
- liver therapy, *Jan*, 242
- posterolateral sclerosis in, management, *Jan*, 245
- severe, electrocardiogram in, *May*, 608
- suspension of discarded erythrocytes in, *March*, 432
- Anemias, macrocytic, *Jan*, 246
- Anesthesia, general, curare in, *March*, 423
- local, new agents, *March*, 419
- surgical, electrocardiogram in, *May*, 614
- Angina pectoris, anoxemia test, *May*, 616
- differential diagnosis, *March*, 513
- testosterone in, *March*, 425
- Ankle clonus in pyramidal tract lesions, *Jan*, 56
- Anoxemia test in angina pectoris, *May*, 616
- Anxiety, later fate of, *May*, 747
- neurosis, in combat crews, *May*, 731
- Aorta, aneurysm, electrocardiograms in, *May*, 605
- Aorta coarctation, electrocardiogram in, *May*, 605, 606
- Appendicitis, chronic, simulating peptic ulcer, *May*, 629
- Army Air Forces, rehabilitation in, *May*, 715
- rheumatic fever in, convalescent care, *May*, 765
- Army, fatigue and exhaustion states in, *May*, 771
- reconditioning programs, *May*, 788
- Arrhythmias, digitalis in, *March*, 531
- quinidine in, *Jan*, 216
- Arthritis, physical medicine in, *May*, 790
- rheumatoid, etiology, environmental factors, *May*, 566
- neostigmine in, *March*, 423
- Aspiration biopsy of liver, *March*, 365
- Aspirin, blood coagulation and, *March*, 430
- Asthma, bronchial, complications, unusual, *March*, 456
- military service and, *March*, 455
- recent advances, *March*, 453
- treatment, *March*, 458, 461
- Auricular fibrillation, digitalis in, *March*, 532
- quinidine in, *Jan*, 217
- flutter, digitalis in, *March*, 532
- quinidine in, *Jan*, 223
- Axillary nerve injuries, *Jan*, 23
- BABINSKI sign in pyramidal tract lesions, *Jan*, 47
- Back strain, *May*, 568
- Barbiturates in war psychoses, *March*, 418
- Bed rest in convalescence, undesirable effects, *May*, 720, 748, 809
- Behavior Clinic of criminal court, *Jan*, 202
- Benzedrine in prevention of motion sickness, *March*, 418
- Beriberi, diet in, *May*, 803
- Biopsy, endometrial, *Jan*, 252
- in lymphogranuloma venereum, *May*, 678
- liver, by aspiration, *March*, 365
- Bladder atony, furmethide in, *March*, 421
- Blastomycosis, *March*, 334
- Blood coagulation, drugs influencing, *March*, 430
- loss, acute, electrocardiogram in, *May*, 613
- Bones, lesions, in hyperparathyroidism, *March*, 394, 396

Brachial plexus injuries *Jan.*, 19  
Bromsalizol, *March* 419  
Bronchial asthma recent advances, *March*, 453  
Bronchopneumonia penicillin in case report, *May* 580  
Brucella *March* 359  
Brucellosis *March*, 343  
penicillin failure in *May*, 586  
Buboes, inguinal in lymphogranuloma venereum *May*, 668  
Bubonell *May*, 669 670  
Burns shock in, sodium lactate in *March* 438

CANDIDA albicans infections with, *March* 323  
Carbon dioxide in bronchial asthma, *March* 459  
Carcinoma of prostate estrogen therapy, *March*, 435  
of stomach, diagnosis, *March*, 489  
gastroscopy in, *March*, 499  
Cataplexy potassium chloride in *March*, 422  
Catarrh, gastric, with peptic ulcer *May*, 628  
Causalgia *Jan.*, 13  
Cavernostomy in tuberculosis, *March*, 450  
Cedilanid *March*, 424 529  
Cellulitis penicillin in *May* 584  
Cerebral palsies of children rehabilitation in, *May*, 792 819  
Chaddock's sign in pyramidal tract lesions, *Jan.*, 50  
Chemotherapy in brucellosis, *March*, 357  
in lymphogranuloma venereum *May*, 682  
in tuberculosis, *March* 445  
in urinary tract infections *May*, 574, 575  
Cholesterothorax, *March* 507 510  
Choline in cirrhosis of liver *March*, 429, 484  
Chordotomy for intractable pain, *Jan.*, 93  
Choriomeningitis lymphocytic, *Jan.*, 36  
Chromoblastomycosis *March* 296  
Chylothorax, *March* 526 537  
Circus movement, *Jan.*, 216  
Cirrhosis of liver correction of compensated liver function study with liver biopsy *March* 377  
diagnosis, *March* 453  
dietary treatment - *March*, 376, 421, 484 485 *May* 600  
etiology *March*, 273 451  
lipotropic substances in, *March*, 422, 484 *May* 600  
nutritional deficiency in *May*, 655

Cirrhosis of liver, symptoms and signs *March*, 275  
treatment recent advances, *March*, 273 479  
Clawed hand in ulnar nerve injury, *Jan.*, 15  
Clonus in pyramidal tract lesions *Jan.*, 56  
Coccidioidin, *March*, 334  
Coccidioidomycosis, *March*, 332  
Cold, common propadrine hydrochloride in *March*, 420  
Colitic chronic ulcerative, sulfathiazidine in *March* 427  
Colon diverticulitis and diverticulosis, clinical study *May*, 639  
Complement fixation test in lymphogranuloma venereum, *May*, 678  
Convalescence bed rest in, undesirable effects, *May*, 720 748, 809  
in home, rehabilitation problems, *May*, 818  
in hospital rehabilitation problems, *May*, 808  
Convalescent care of rheumatic fever in Army Air Forces *May*, 765  
hospital, Army Air Forces, role of, *May*, 721  
training program, Army Air Forces, *May*, 716  
wart need for, *May*, 812  
Coronary occlusion, quinidine in, *Jan.*, 227  
restriction of activity in, and extent of myocardial infarction, *March*, 405  
thrombosis, electrocardiogram in, *May*, 598  
pain of, differential diagnosis, *March*, 413  
Criminal responsibility, epilepsy and, *Jan.*, 212  
insanity and, *Jan.*, 197  
mental retardation and, *Jan.*, 208  
Cryptococcosis, *March*, 335  
Cure, new ones, *March*, 423  
text for myasthenia gravis, *Jan.*, 129  
Cystitis in liver disease, *March*, 424  
D. urexymycinum hydrochloride, *March*, 429  
Defective diagnosis, rehabilitation problems, *May*, 794  
Demencia senilis, *Jan.*, 147  
Dermoid, *March*, 417  
Disinfection in clinical cases, *May*, 732  
in returned soldiers, *May*, 736  
Disinfectants, *March*, 423  
Dissociation, *March*, 326  
Dyslipoproteinemia in patients in *March*, 422  
Dyslipoproteinemia, *March*, 422  
Dyslipoproteinemia, *March*, 422  
Dyslipoproteinemia, *March*, 422



- Diabetic coma, electrocardiogram in, *May*, 608
- Diasone in tuberculosis, *March*, 447, 448
- Dichlorophenarsine hydrochloride in syphilis, *March*, 438
- Dicoumarol in prevention of embolism and thrombosis, *March*, 430, 431
- Dienoestrol, *March*, 435
- Diet in cirrhosis of liver, *March*, 276, 427, 484, *May*, 655
- in nutritional deficiencies, *May*, 799-802
- in peptic ulcer, fundamental importance, in Army hospital, *May*, 706
- in pernicious anemia, *Jan*, 244
- in rehabilitation, *May*, 794
- Diglanid, *March*, 423
- Digitaline nativele, *March*, 423
- Digitalis, blood-clotting and, *March*, 431
- effects on electrocardiogram, *May*, 609
- in arrhythmias, *March*, 531
- in heart failure, *March*, 524
- preparations and uses, *March*, 423, 524
- Digitoxin, *March*, 423
- Digoxin, *March*, 424, 529
- Dihydratachysterol in hyperparathyroidism, *March*, 402
- Dilantin sodium in bronchial asthma, *March*, 459
- Diuretics, new, *March*, 424
- Diverticulitis of colon, *May*, 639
- Diverticulosis of colon, clinical study, *May*, 639
- Drop wrist in radial nerve injury, *Jan*, 10
- Dysentery, bacillary, sulfasuxidine in, *March*, 426
- sulfathalidine in, *March*, 426
- Dysmenorrhea, hormone therapy, *Jan*, 259, 262, 265, 267
- EDUCATIONAL retraining in Army Air Forces, *May*, 721
- Electrocardiography, uses in medicine, *May*, 590
- ventricular gradient in, *March*, 464
- Electrodiagnosis in peripheral nerve injuries, *Jan*, 23
- Electroshock therapy in psychoses with insomnia, *Jan*, 192
- outpatient, in psychiatric disorders, *Jan*, 165
- Embolism, prevention, dicoumarol in, *March*, 430, 431
- heparin in, *March*, 431
- pulmonary, prevention, exercises for, *May*, 789
- Emotions, neurophysiology of, *May*, 744
- Empyema, pyogenic, *March*, 507, 510
- Encephalo-melo-radiculoneuritis, acute, *Jan*, 1
- Endocarditis, bacterial, subacute, penicillin in, *May*, 583
- brucella, *March*, 348
- subacute bacterial, therapeutics, *March*, 425
- Endocrine system, therapeutics, *March*, 433
- therapy in menstrual disorders, *Jan*, 251
- Endometrial biopsy, *Jan*, 252
- Enuresis, ephedrine in, *March*, 420
- Ephedrine in enuresis, *March*, 420
- in myasthenia gravis, *Jan*, 134, *March*, 421
- Epidermatophytosis, *March*, 323
- Epilepsy, criminal responsibility and, *Jan*, 212
- electrocardiogram in, *May*, 608
- glutamic acid in, *March*, 418
- Erb's paralysis in brachial plexus injuries, *Jan*, 19
- Erythrocytes, discarded, suspension of, clinical uses, *March*, 432
- Esthiomene, *May*, 670
- Estrogen therapy in menstrual disorders, *Jan*, 259
- in prostatic cancer, *March*, 435
- new products, *March*, 435
- Ether in oil, intramuscularly, in bronchial asthma, *March*, 459
- Ethinyl estradiol, *March*, 435
- Exercises in pulmonary embolism prevention, *May*, 789
- therapeutic, in convalescence, *May*, 787, 810
- Exhaustion states in Army and in industry, *May*, 771
- Expectorants in bronchial asthma, *March*, 458
- Extrasystoles, quinidine in, *Jan*, 227
- Eye signs in brucellosis, *March*, 347
- FACIAL pain, neoplasia as cause, *Jan*, 91
- relief of, *Jan*, 73
- symptomatic, *Jan*, 87
- Fasciculation, neostigmine in, *March*, 422
- Fatigue, "operational," *May*, 729
- states in Army and in industry, *May*, 771
- Fear, electrocardiographic changes induced by, *May*, 618
- Feeble-mindedness, criminal responsibility and, *Jan*, 208
- Feet, dermatophytosis of, *March*, 323
- Femoral nerve injuries, *Jan*, 23
- Ferrous carbonate in facial pain, *Jan*, 77
- Fever therapy in brucellosis, *March*, 360
- Fibrin foam and film in neurosurgery, *March*, 432
- Fibrositis, etiology, environmental factors, *May*, 568

- Fluorescence test for dermatophytosis, *March* 325
- Fractures in hyperparathyroidism, *March* 394
- Fret test *May* 677
- inverted *May*, 678
- Friedreich's disease, electrocardiogram in *May* 607
- Functional tests electrocardiogram in, *May*, 615
- Fungus infections pleural effusions of *March* 508 511
- sodium propionate in *March*, 438
- Furmetblide in bladder atony *March* 421
- GALLBLADDER disease electrocardiograms in, *May* 606
- Gastric analysis diagnostic value *March*, 492
- Gastritis diagnosis, *March* 489
- gastroscopy in *March* 498
- Gastroduodenal disease diagnosis *March* 489
- Gastrointestinal tract therapeutics *March* 426
- Gastroscopy *March* 497
- Gelatin as substitute for plasma *March* 433
- Globin insulin in diabetes, *March* 436
- Glomerulonephritis, acute in children electrocardiogram in, *May* 606
- penicillin in *May*, 582
- Glomerulosclerosis intercapillary *March* 538
- Glucosides cardiac, *March* 423 529
- Glutamic acid in epilepsy *March* 418
- Glycine in myasthenia gravis, *Jan* 135
- Gonadotropin therapy in menstrual disorders *Jan.*, 256
- Gonda sign in pyramidal tract lesions *Jan* 57
- Gonorrhea, penicillin resistant *May* 688
- Gordon's sign in pyramidal tract lesions *Jan.*, 53
- Gout etiology environmental factors *May* 567
- Grafts nerve *Jan.*, 27
- Groin dermatophytosis of *March* 323
- Guanidine in myasthenia gravis *Jan* 134
- Guillain Barré syndrome *Jan* 1
- HEADACHE, tension *May* 568
- Heart disease electrocardiograms in *May* 595
- pain of, differential diagnosis *March* 513
- quinidine in *Jan.*, 215
- failure congestive with hypertension *March* 542
- digitalis in, *March* 524
- Heart Irregularities, electrocardiograms in *May*, 590
- lesions in hyperparathyroidism, *March* 395
- position electrocardiogram and, *May*, 608
- structural abnormalities electrocardiograms in *May* 595
- therapeutics *March*, 423
- Heat therapy in rehabilitation *May* 787
- Hematoma subdural, *Jan.*, 62
- Hemolytic anemia, acute acquired, *May*, 695
- Hemorrhage in liver damage control of, *March* 432
- Hemothorax *March* 506 510
- Heparin in thrombosis and embolism *March*, 431
- Herniation of intervertebral disk *Jan* 111
- Hexestrol *March* 435
- Histamine azoprotein in bronchial asthma *March* 460
- in migraine, *March* 438
- Histoplasmosis, *March* 337
- Hoffman sign in pyramidal tract lesions, *Jan.*, 54
- Hormone assays *Jan.*, 254
- Hospitalization intramural need for, *May* 812
- Hospitals, civilian rehabilitation problem in *May*, 808
- rehabilitation possibilities in postwar *May* 725
- Hostile aggressive reactions in returned soldiers *May* 735
- Hydrochloric acid in pernicious anemia, *Jan* 243
- Hydrothorax *March* 506 510
- Hyoscine in prevention of motion sickness, *March* 418
- Hyperparathyroidism *March* 389
- Hyperpyrexia. See *Fever therapy*
- Hypertension, arterial kidneys and clinical relationships *March* 535
- drug therapy, *March* 425
- Hyperthyroidism, thiouracil in *March* 302 433
- Hypnotics in insomnia *Jan* 187
- Hypocalcemia electrocardiograms in *May*, 613
- Hypomenorrhea hormone therapy *Jan* 260
- Hypoparathyroidism, treatment, *March* 434 435
- Hypotension neosynephrin hydrochloride in *March* 420
- IXANTHINE serum in brucellosis *March* 359
- Industry fatigue and exhaustion states in *May* 771
- Inguinal buboes *May* 668

- Injuries, peripheral nerve, *Jan*, 9  
 Insanity and the criminal, *Jan*, 195  
   legal conceptions, *Jan*, 204  
   malinger and, *Jan*, 205  
 Insomnia, *Jan*, 178  
   causes of, *Jan*, 180  
   clinical effects, *Jan*, 181  
   general management, *Jan*, 184  
   hypnotics in, *Jan*, 187  
   psychotherapy, *Jan*, 186  
   shock therapy in psychotic cases, *Jan*, 192  
 Insulin, globin, in diabetes, *March*, 436  
   shock therapy in psychoses with insomnia, *Jan*, 192  
 Internal medicine in general practice, symposium on, *May*, 563  
 Intervertebral disk, protrusion of, *Jan*, 111  
 Intocostrine, *March*, 423  
 Iodides in sporotrichosis, *March*, 330  
 Iodine in hyperthyroidism, thiouracil and, *March*, 310  
 JOLLY's myasthenic reaction, *Jan*, 129  
 KEPHINE hydrochloride, *March*, 420  
 Kidneys, arterial hypertension and, clinical relationship, *March*, 535  
   infections, nontuberculous, treatment, *May*, 571  
   lesions, in hyperparathyroidism, *March*, 394  
 Klumpke's paralysis in brachial plexus injuries, *Jan*, 19  
 LANATOSIDE C, *March*, 424  
 Lead poisoning, sodium citrate in, *March*, 437  
 Lederer's anemia, *May*, 702  
 Lipotropic substances in cirrhosis of liver, *March*, 428, 483, *May*, 658  
 Liver, biopsy, by aspiration, *March*, 365  
   cirrhosis See *Cirrhosis of liver*  
   damage to, hemorrhage in, control of, *March*, 432  
   diseases, diet as factor, *March*, 276, 427, 484  
   functional tests, composite, *March*, 363  
   therapy in pernicious anemia, *Jan*, 242  
 Lobectomy in tuberculosis, *March*, 451  
 Lumbago, etiology, *May*, 568  
 Lung, resection, in tuberculosis, *March*, 451  
 Lymphocytic choriomeningitis, benign, *Jan*, 36  
 Lymphogranuloma venereum, *May*, 663  
   diagnosis, *May*, 677  
   extragenital, *May*, 675  
   treatment, *May*, 682  
 Lymphorrhoids in lymphogranuloma venereum, *May*, 670, 671  
 MAGNESIUM sulfate in paroxysmal tachycardia, *March*, 426  
 Maladjustment, transitory, in soldiers, reconditioning in, *May*, 751  
 Malaria, reconditioning the patient, *May*, 760  
 Malinger of insanity to escape criminal responsibility, *Jan*, 205  
 Malta fever See *Brucellosis*  
 Mandelic acid in urinary tract infections, *May*, 574, 576  
 Massage in rehabilitation, *May*, 787  
 Mecholyt, effects on electrocardiogram, *May*, 614  
   in bronchial asthma, *March*, 459  
 Median nerve injuries, *Jan*, 11  
 Median-ulnar nerve injuries, *Jan*, 18  
 Medullary tractotomy for facial pain, *Jan*, 84  
 Meigs' syndrome, pleural effusion in, *March*, 509, 512  
 Meningitis, lymphocytic, benign, *Jan*, 63  
   pneumococcal, penicillin in, *May*, 585  
 Menorrhagia, hormone therapy, *Jan*, 259, 261, 264, 266  
 Menstruation, disorders of, diagnostic aids, *Jan*, 252  
   endocrine therapy, *Jan*, 251  
 Mental disease, criminal responsibility and, *Jan*, 195  
   retardation, criminal responsibility and, *Jan*, 208  
 Mercupurin as diuretic, *March*, 424  
 Methenamine in urinary tract infections, *May*, 574, 575  
 Methionine in cirrhosis of liver, *March*, 429, 484  
 Microsporon infections, *March*, 323  
 Migraine, histamine-azoprotein in, *March*, 438  
 Miscarriage See *Abortion*  
 Monilia albicans, infections with, *March*, 323, 328  
 Monoacetylmorphine, *March*, 418  
 Monocaine for local anesthesia, *March*, 419  
 Motion sickness, treatment, *March*, 418  
 Mouth wash in pernicious anemia, *Jan*, 245  
 Musculocutaneous nerve injuries, *Jan*, 23  
 Myasthenia gravis, diagnostic tests, *Jan*, 128, *March*, 422  
   management, *Jan*, 126 179  
   treatment, advances in, *March*, 421  
 Myasthenic reaction of Jolly, *Jan*, 129  
 Mycology, medical, *March*, 323  
 Myocardial infarction, restriction of activity in coronary occlusion in relation to, *March*, 405  
 Myocarditis, Fiedler's, electrocardiogram in, *May*, 606

- NARCOSYNTHESIS in war neurosis, *May*  
787
- Neck painful *May* 468
- Needle liver biopsy *March* 354
- Neosphenamine in urinary tract infections, *May* 577
- Neostigmine in fasciculation *March* 422  
in myasthenia gravis, diagnostic, *March*  
422  
therapeutic, *March* 421  
in poliomyelitis, *March* 423  
in rheumatoid arthritis *March*, 423
- Neosynephrin hydrochloride, uses *March*  
470
- Nephrocalcinosis in hyperparathyroidism,  
*March* 394
- Nephrosis testosterone in, *March*, 475
- Nerve grafts, *Jan.*, 27
- Nerves, peripheral, injuries, diagnosis and  
surgical treatment, *Jan.*, 9
- Nervous disease, organic origin in ap-  
parent functional cases, *Jan.*, 29  
system autonomic, therapeutics, *March*,  
*October* 1952
- Ophthalmia, acute, in children, *Jan.*, 1
- Ophthalmia, acute, in children, *March* 554
- Ocular signs of systemic disease,  
*Jan.*, 1
- Otitis media, acute, in children, *March*,  
259 265
- Osteoarthritis, etiology, experimental  
factors *May* 57
- Oxalate, *March* 424
- Pain, facial, neuropathic cause, *Jan.*,  
51  
relief of *Jan.*, 73  
symptomatic *Jan.*, 8
- Intractable chordotomy for *Jan.*, 1  
precordial, differential diagnosis, *March*,  
513
- Pancreatic carcinoma, early re-  
sponse to *March* 1
- Pancreatic carcinoma, early re-  
sponse to *May*, 1952

- Peptic ulcer, diet in, fundamental importance, in Army hospital, *May*, 706  
 differential diagnosis, *May*, 624  
 gastric catarrh with, *May*, 628  
 gastroscopy in, *March*, 499  
 in asthenic person, *May*, 625  
 in hypersthenic person, *May*, 626  
 roentgen diagnosis, *March*, 493  
 sodium alkyl sulfate in, *March*, 426  
 vitamin "U" therapy, *May*, 709  
 with atypical symptoms, *May*, 625
- Periarteritis nodosa, *Jan*, 139
- Pericarditis, acute, electrocardiograms in, *May*, 603  
 chronic constrictive, electrocardiograms in, *May*, 604, 609
- Peripheral nerve injuries, diagnosis and surgical treatment, *Jan*, 9
- Peritoneoscopy in liver disorders, *March*, 369
- Pernicious anemia, *Jan*, 229  
 clinical types, *Jan*, 230  
 liver therapy, *Jan*, 242  
 posterolateral sclerosis in, management, *Jan*, 245
- Peroneal nerve injuries, *Jan*, 20
- Personality patterns, *May*, 746
- Pharmacology, recent advances, *March*, 417
- Phthalylsulfathiazole See *Sulfathaladine*
- Physical fitness testing of rheumatic fever patients, *May*, 719  
 medicine, in arthritis, *May*, 790  
 in cerebral palsy, *May*, 792, 819  
 in hospital organization, place of, *May*, 816  
 in poliomyelitis, *May*, 791  
 in rehabilitation, *May*, 786  
 in thrombo-angitis obliterans, *May*, 790  
 in tuberculosis, *May*, 792  
 preventive, *May*, 788  
 rehabilitation, in Army Air Forces, *May*, 717  
 training, of rheumatic fever patients, *May*, 768
- Plasma, bovine, for human use, *March*, 433
- Pleura, malignant tumors, effusions due to, *March*, 509, 512
- Pleural effusions, diagnosis and treatment, *March*, 502
- Pneumectomy in tuberculosis, *March*, 451
- Pneumonia, penicillin in, *May*, 580, 582  
 pneumococcal, sulfamerazine in, *March*, 294  
 postoperative, prevention, breathing exercises for, *May*, 789
- Poliomyelitis, physical medicine in, *May*, 791  
 neostigmine in, *March*, 423
- Polyuria in hyperparathyroidism, *March*, 395
- Potassium chloride in cataplexy, *March*, 422  
 in myasthenia gravis, *Jan*, 135  
 salts, effects on electrocardiogram, *May*, 613
- Pourodigin, *March*, 423
- Precordial pain, differential diagnosis, *March*, 513
- Pre-eclampsia, *March*, 538, 541
- Pregnancy, macrocytic anemia of, *Jan*, 247
- Procaine hydrochloride for local anesthesia, *March*, 419
- Proctitis in lymphogranuloma venereum, *May*, 673
- Progesterone therapy in menstrual disorders, *Jan*, 263
- Promin in tuberculosis, *March*, 447, 448
- Propadrine hydrochloride in coryza, *March*, 420
- Propionate-propionic acid ointment in dermatophytosis, *March*, 326
- Prostate, carcinoma, estrogen therapy, *March*, 435
- Prostigmine in myasthenia gravis, *Jan*, 131  
 diagnostic test, *Jan*, 128
- Protrusion of intervertebral disk, *Jan*, 111
- Psychiatric disorders in combat crews overseas, *May*, 729  
 in returnees, *May*, 733
- Psychiatrist, function of, in court, *Jan*, 211
- Psychological readjustment in rehabilitation program, Army Air Forces, *May*, 723
- Psychoneurosis, transitory, in soldiers, reconditioning in, *May*, 751
- Psychoses, criminal responsibility in, *Jan*, 195  
 electroshock therapy, outpatient, *Jan*, 165  
 war, harbiturates in, *March*, 418  
 with insomnia, electroshock and insulin shock therapy, *Jan*, 192
- Psychosomatic aspects of rehabilitation, *May*, 740  
 principles, *May*, 742  
 states, in combat crews, *May*, 732  
 in returned soldiers, *May*, 736
- Psychotherapy in fatigue and exhaustion states, *May*, 781  
 in insomnia, *Jan*, 186  
 in war neuroses, *May*, 737
- Psychotic-like states in combat crews, *May*, 732  
 in returned soldiers, *May*, 736
- Pulmonary embolism, electrocardiograms in, *May*, 605

- Pulmonary embolism prevention exercises for *May*, 789
- Pulsus alternans, electrocardiogram in, *May*, 617
- Pylonephritis, atrophic, *March*, 541  
in hyperparathyroidism *March*, 394
- Pyramidal tract signs pathologic *Jan* 45
- QUINIDINE, effects on electrocardiogram *May*, 611  
in auricular fibrillation *Jan* 217  
in auricular flutter *Jan.*, 223  
in paroxysmal tachycardia, *Jan.*, 226  
uses and abuses, *Jan* 215
- Quinine test for myasthenia gravis, *Jan.*, 129 *March* 422
- RACEPHEDRINE hydrochloride, *March* 420
- Radial nerve injuries *Jan*, 10
- Radiculoneuritis, acute infectious *Jan*, 1
- Reconditioning of malaria patient *May*, 760  
of transitorily maladjusted soldiers, *May* 751  
program Army, *May* 788  
Army Air Forces *May*, 717
- Rectum stricture, in lymphogranuloma venereum *May* 673 674 683
- Rehabilitation in Army Air Forces *May* 715  
in civilian medical practice, *May* 807  
in *May*, 817
- Federal State and industry's interest nutrition in *May* 794  
of malaria patient, *May* 760  
of rheumatic fever patients *May* 765  
of transitorily maladjusted soldiers *May* 751  
physical medicine in *May* 786  
postwar possibilities, *May* 725  
psychosomatic aspects, *May* 740  
symposium on *May* 714
- Retrogasserian neurotomy classical for facial pain *Jan.*, 80  
posterior for facial pain *Jan* 83
- Returnees, psychiatric disorders in *May* 733
- Rheumatic conditions, etiology environmental factors, *May* 566
- Rheumatic fever convalescence, physical fitness testing and physical training in *May* 719  
in Army Air Forces, convalescent care *May* 765  
penicillin failure in *May* 580  
pleural effusion in, *March* 508  
sodium salicylate in *March* 425  
sulfadiazine in, prophylactic *March* 425
- Rheumatoid arthritis, etiology environmental factors *May* 566  
neostigmine in *March* 423
- Riboflavin deficiency diet in *May* 803
- Ringworm *March*, 323
- Roentgen diagnosis of carcinoma of stomach, *March* 495  
of peptic ulcer *March*, 493  
of tuberculosis rapid creening methods *March*, 544
- Rossolimo sign in pyramidal tract lesions, *Jan* 53
- SALYRGAN - THEOPHYLLINE as diuretic, *March*, 424
- Sandoz, *March*, 424
- Scalp dermatophytosis of *March* 323
- Schizophrenia, *Jan*, 150  
modern concept of *Jan.*, 147
- Sciatic nerve injuries *Jan.*, 20
- Sciatica, *May*, 569
- Sclerosis, posterolateral management in pernicious anemia *Jan.*, 245
- Scurvy diet in *May* 803
- Sedatives in psychosomatic disorders, abuse of *May* 748
- Shock in burns, sodium lactate in *March* 438  
therapy of psychoses *Jan* 165  
prevention of fractures, curare for, *March*, 423
- Shoulder painful *May* 569
- Sign of the groove in lymphogranuloma venereum *May* 668 669
- Silicosis, aluminum powder in, *March* 437
- Skin test in brucellosis *March* 354
- Sleeplessness, *Jan*, 178  
clinical effects, *Jan* 181  
treatment, *Jan* 184
- Sodium alkyl sulfate in peptic ulcer *March*, 426  
citrate in lead poisoning *March* 437  
lactate in burn shock *March* 438  
propionate in fungus infections, *March* 438  
salicylate in rheumatic fever *March* 425  
sulfanilyl sulfanilate in lymphogranuloma venereum *May* 682
- Soldiers, combat psychiatric disorders in *May*, 729  
returned from combat, psychiatric disorders in *May* 733  
transitorily maladjusted reconditioning of, *May* 751  
veteran psychosomatic disorders in *May*, 740
- Spiller Frazier operation for facial pain *Jan.*, 80
- Splenectomy in hemolytic anemia *May* 704
- Spondylitis brucella, *March* 351
- Sporotrichosis, *March* 328
- Steam inhalations in bronchial asthma, *March* 458

- Steatorrhea, pancreatic, pancreatic enzyme in, *March*, 429
- Sterility, hormone therapy, *Jan*, 258, 261
- Stomach, carcinoma, diagnosis, *March*, 489
- Streptotrichosis, *March*, 340
- Strophanthin in heart failure, *March*, 529
- Subdural hematoma, *Jan*, 62
- Succinylsulfathiazole See *Sulfasuxidine*
- Sulfadiazine in lymphogranuloma venereum, *May*, 682
- in rheumatic fever, prophylactic, *March*, 425
- in urinary tract infections, *May*, 576
- Sulfamerazine in pneumococcal pneumonia, *March*, 294
- Sulfasuxidine in bacillary dysentery, *March*, 426
- Sulfathalidine in bacillary dysentery, *March*, 426
- in chronic ulcerative colitis, *March*, 427
- Sulfathiazole in lymphogranuloma venereum, *May*, 682
- in urinary tract infections, *May*, 576
- Sulfonamides in brucellosis, *March*, 357
- in lymphogranuloma venereum, *May*, 682
- in tuberculosis, *March*, 447
- in urinary tract infections, *May* 574, 576
- insoluble, in intestinal diseases, *March*, 426
- versus penicillin, *May*, 579
- Suprapatellar reflex in pyramidal tract lesions, *Jan*, 57
- Suture, primary, in peripheral nerve injuries, *Jan*, 25
- Sympathomimetic drugs, new, *March*, 419
- Syphilis, cardiovascular, electrocardiogram in, *May*, 606
- dichlorophenarsine hydrochloride in, *March*, 438
- TACHYCARDIA, paroxysmal, digitalis in, *March*, 531
- magnesium sulfate in, *March*, 426
- quinidine in, *Jan*, 226
- Talma operation in cirrhosis of liver, *March*, 281
- Testosterone in menstrual disorders, *Jan*, 265
- in nephrosis, *March*, 436
- Tetanus, curare in, *March*, 423
- Tetany, parathyroid, prevention, *March*, 402, 434
- Thiamine hydrochloride in facial pain, *Jan*, 77
- Thiouracil, clinical development and application, *March*, 303, 306
- in thyrotoxicosis, *March*, 302, 433
- toxicity, *March*, 307
- Thoracentesis, *March*, 503
- Thoracoplasty in tuberculosis, *March*, 449
- Thrombo-angitis obliterans, physical medicine in, *May*, 791
- Thrombosis, coronary, *March*, 405
- pain of, differential diagnosis, *March*, 513
- venous, heparin in, *March*, 431
- Thrush, *March*, 323, 328
- Thymectomy for myasthenia gravis, *Jan*, 136
- Thyroid extract, effects on electrocardiogram, *May*, 611
- in familial periodic paralysis, *March*, 422
- Thyrotoxicosis, thiouracil in, *March*, 302, 433
- Tibial nerve injuries, *Jan*, 22
- Tinea, *March*, 323
- Torulosis, *March*, 335
- Tractotomy, medullary, for facial pain, *Jan*, 84
- Transfusions, blood, in hemolytic anemia, *May*, 703
- in pernicious anemia, *Jan*, 245
- Trends, modern, in internal medicine, *May*, 563
- Trichinosis, electrocardiogram in, *May*, 607
- Trichlorethylene in facial pain, *Jan*, 77
- Trichophytin test for dermatophytosis, *March*, 325
- Trichophytosis, *March*, 323
- Trigeminal neuralgia, *Jan*, 73
- atypical, *Jan*, 85
- symptomatic, *Jan*, 75
- Trigger zones in trigeminal neuralgia, *Jan*, 74
- Tromner's technic for Hoffmann sign, *Jan*, 54
- Tuamine sulfate, *March*, 420
- Tuberculosis, physical medicine in, *May*, 792
- pulmonary, asymptomatic case, management, *March*, 550
- chemotherapy, *March*, 445
- diasone in, *March*, 447, 448
- modern methods of finding, *March*, 544
- penicillin failure in, *May*, 587
- pleural effusions of, *March*, 507, 511
- promin in, *March*, 447, 448
- surgical treatment, *March*, 449
- treatment, recent advances, *March*, 445
- Tularemia, pleural effusion in, *March*, 508
- Tumors, facial pain due to, *Jan*, 91
- ULNAR nerve injuries *Jan*, 15
- Ulnar-median nerve injuries, *Jan*, 18
- Undecylenate-undecylenic acid ointment in dermatophytosis, *March*, 326

- Undulant fever See *Brucellosis*
- Urgin in heart failure *March*, 529
- Urinary tract infections, chemotherapy  
     *May*, 514 575  
     nontuberculous, treatment, *March*  
         571
- Uterine bleeding functional hormone  
     therapy *Jan.*, 259 261 264, 265
- VACCINES in brucellosis, *March*, 353  
     in lymphogranuloma venereum, *May*  
         683
- Ventricular gradient *March*, 464
- Ventrol, *March* 420
- Vesania *Jan.*, 147
- Vitamin A deficiency, diet in, *May*, 851
- Vitamin B deficiency diet in, *May*, 851  
     electrocardiograms in, *May* 851





*This edition is produced in compliance with the Government's regulations for conserving paper and other essential materials*

## CONTENTS

### SYMPOSIUM ON MEDICAL EMERGENCIES

	PAGE
Nonsurgical Emergencies Encountered in the Practice of Dermatology By Dr Paul A. O'Leary	833
Nonsurgical Emergencies in Cases of Thoracic Disease By Dr Herman J Moersch	837
Nonsurgical Emergencies in Obstetrics By Dr John E. Faber	848
Emergencies Associated with the Thymus By Drs. Roger L. J Kennedy and Gordon B New	860
Nonsurgical Emergencies of the Respiratory Tract in Childhood By Dr George B Logan	864
Cardiac Emergencies in Pediatric Practice By Dr Haddow M Keith	871
Management of Nonsurgical Emergencies Associated with the Urinary Tract of Children By Dr Roger L. J Kennedy	874
Acute Nonsurgical Emergencies Related to the Gastro-intestinal Tract By Dr George B Logan	878
Nonsurgical Neurologic Emergencies in Childhood By Dr Haddow M Keith	886

### CLINICS ON OTHER SUBJECTS

Postwar Aspects of Some Tropical Diseases By Dr George G Stilwell	897
Penicillin Methods of Administration and Dosage By Dr Wallace E. Herrell	909

	PAGE
Observations on Chemotherapy of Clinical and Experimental Tuberculosis By Drs H Corwin Hinshaw and William H Feldman	918
Rheumatic Fever a Summary of Present-day Concepts By Dr Arlie R Barnes	923
The Clinical Use of Dicumarol By Dr Nelson W Barker	929
Clinical Significance of the Erythrocyte Sedimentation Rate By Dr Donald R Nichols	936
The Diagnosis of Raynaud's Disease By Dr Edgar A Hines, Jr	942
The Effect of Smoking Cigarets and the Intravenous Administration of Nicotine on the Heart and Peripheral Blood Vessels By Dr Grace M Roth, Captain John B McDonald and Dr Charles Sheard	949
Iron Deficiency and Anemia Associated with Carcinoma of the Proximal Portion of the Colon By Drs R Lee Clark, Jr, Marschelle H Power, Frank J Heck and Claude F Dixon	958
Tests of Liver Function By Dr James F Weir	973
Constitutional Hepatic Dysfunction By Dr Mandred W Comfort	982
Differential Diagnosis of Nephritis By Dr Melvin W Binger	990
Chronic Cervicitis By Dr Monte C Piper	998
Certain Conditions of the Female Urethra By Drs Edward N Cook and Jane E Hodgson	1005
Real Versus Supposed Disturbances of the Endocrine Glands By Dr Edward H Rynearson	1009
The Diagnosis of Primary Hyperparathyroidism By Dr F Raymond Keating, Jr	1019
Protection in Roentgenoscopy By Drs John F Bacon and Eugene T Leddy	1036
The Importance of Diagnosing Chronic Subdural Hematoma By Drs Philip H Heersema and John G Freeman	1042

## CONTENTS

Cirrhosis of the Liver Presenting the Clinical Features of Xanthomatous Biliary Cirrhosis, But with Confirmation at Autopsy (Follow up of Case Reported Previously)	1054
By Drs F W Hoffbauer, G T Evans and C. J Watson, Minneapolis	
Cumulative Index	1056



# THE MEDICAL CLINICS of NORTH AMERICA

---

MAYO CLINIC NUMBER

---

## SYMPOSIUM ON MEDICAL EMERGENCIES

---

### NONSURGICAL EMERGENCIES ENCOUNTERED IN THE PRACTICE OF DERMATOLOGY

PAUL A. O'LEARY

ALTHOUGH there are but few diseases of the skin which may be classified as actual emergency conditions, nevertheless, there are several forms of dermatitis of the acute inflammatory type in which the therapeutic measures should be employed as promptly as possible after the diagnosis has been made. When these agents are specific in their effect, their immediate use becomes essentially an emergency procedure.

#### ACUTE DERMATITIS

Although an acute inflammation of the skin characterized by erythema, edema, vesiculation and sometimes bullous formation may be due to a variety of etiologic agents, it is advisable to apply the therapeutic efforts immediately and postpone the effort to determine the cause of the dermatitis until the acute reaction has subsided. The reason for so doing is that the search for the cause of an acute dermatitis usually requires the use of the "patch test" and if the irritating substance which caused the dermatitis is applied to the skin the dermatitis may be severely aggravated and extended. It is well to bear in mind that a skin which is the site of an acute vesicular reaction as the result of contact with some irritating substance has become highly sensitive, and during the acute phase of irritation it will react unfavorably to substances it tolerated readily in a normal state. This not only applies to the area involved but is to be noted also on almost any part of the patient's skin. This fact is of significance in the consideration of the local therapeutic applications to be employed. While on the subject of hypersensitivity the mechanism of which is not thoroughly understood, comment will be made on the significance hypersensitivity plays in the result of the local measures used in the treatment of acute

dermatitis This is frequently noted in a case in which a patient consults a physician shortly after the onset of the dermatitis and the wet dressings applied give no comfort The use as wet dressings of three or four different medicaments in weak solutions for several days likewise fails to relieve the annoying itching, and all the while the dermatitis is extending and becoming more severe This failure to respond to treatment is frequently the result of the increasing hypersensitivity and it is during this period that the local use of strong applications will aggravate and extend the condition and, likewise, the use of preparations well tolerated by most patients may afford no relief When one switches back and forth between the mild wet dressings used in weak dilutions four or five days or longer may be required for the dermatitis to reach its peak and it is the last application employed that is usually given the credit for controlling the dermatitis while, in reality, the improvement is the result of the hypersensitization process having reached its peak Most of the local applications which previously failed will now be found to be comforting to the patient The recognition of this phenomenon is of utmost importance in the care of a patient with an acute vesicular dermatitis, of contact origin, especially as it applies to the selection of the drugs and the manner in which they are applied to the skin

A skin which is the site of an acute inflammatory reaction with vesiculation, pustules, oozing and crusting is seldom helped by a greasy or oily application because the serum produces a film which prevents the drug from coming in contact with the skin It is in such situations that the use of a wet dressing of a weak astringent or mild antiseptic solution is indicated Among such applications the following have gained popularity because of their demonstrated value solution of aluminum subacetate 0.5 per cent, potassium permanganate solution 1:15,000, boric acid solution 5 per cent, silver nitrate solution 0.1 per cent, and physiologic salt solution 0.9 per cent

There are several factors in the application of a wet dressing that are essential to its successful use First and foremost, the dressing must be kept wet continuously This is accomplished by using a large amount of gauze held on by a bandage which is not too tightly applied and is not covered by an impervious dressing unless heat is to be applied The upper and lower ends of the gauze should be loose enough so that the solutions can be easily and frequently applied at the openings rather than poured on the middle of the bandaged area where most of it is not absorbed by the gauze but runs off the bandage onto the floor or bed It is advisable to remove the entire dressing every three or four hours and aerate the gauze by fluffing or agitating it and, if there is much pus present, a complete change of the gauze should be made three or four times in twenty-four hours The skin may become macerated if the dressing is kept on too long or is too wet, therefore, the dressings should be removed for fifteen to thirty minutes every twelve hours to allow the skin to "dry out" The failure

of a wet dressing to produce relief when properly applied may be due to one of the following factors the solution may be too strong, its pH may be too high or too low, or the dermatitis still may be in the process of spreading. When such situations arise, the type of the application should be changed or weaker dilutions used and a mild sedative employed. As the vesiculation and edema subside and the process becomes less acute, the wet dressings may be discontinued and a mild grease applied. The following ointments may be used in this phase of the disease: 3 per cent ichthyol in zinc oxide, 3 per cent ichthyol in aquaphor, equal parts of aquaphor and lime water, or calamine lotion followed, when it has dried, by boric acid ointment.

Frequently, if the dermatitis has completely reached the subacute phase, the switch to the ointment can be made without discomfort, on the other hand, if the dermatitis is still acute, the ointment may cause discomfort, in which case it is advisable to return to the use of the wet dressing for two or three periods of two or three hours each. It is only in the late or chronic phase that stimulating applications should be employed, and then it is advisable to use them in weak strengths. Either 1 per cent of salicylic acid, 1 per cent of benzoic acid, 1 per cent of *pix liquida*, or 1 per cent of *liquor carbonis detergens* may be incorporated in a suitable base during this phase of the disease.

When the dermatitis has subsided, search may be made for the offending agent by the patch test, that is by applying small amounts of the suspected substance to the skin. This procedure must be used with some caution because, if a large amount of the substance in a strong dilution is applied to the skin it may cause a considerable aggravation of the dermatitis. The patch test is not always specific even though the substances which caused the dermatitis are applied. Certain substances, even in weak strengths, also may produce a 'burn' rather than a specific vesicular reaction. Experience with the procedure and with a large number of substances is necessary to evaluate the test properly. It is unfortunate that the cause of acute vesicular dermatitis cannot be determined in every case.

#### USE OF PENICILLIN

The following acute inflammatory diseases of the skin are materially helped by the use of penicillin, in fact, in several of them the result may be said to be specific because the effect is so rapid and complete.

**Anthrax**—This is a disease usually found in persons who handle hides, hair wool or the carcasses of animals. A small epidemic which occurred in this country in 1919 was due to infected shaving brushes that had been imported.

The initial lesion, usually single, appears as a single papule which soon develops a bullous center. The reaction rapidly becomes very intense, the bullae rupture and a dark sphacelus results, while groups of vesicles or pustules develop around the periphery of the original lesion, which has now become markedly indurated.



The constitutional symptoms may be severe and consist of fever, delirium and prostration. Death may occur from septicemia or the constitutional symptoms may be mild and insignificant.

The diagnosis is readily made by recognition of the bacillus anthracis in smears taken from the pustule. Treatment consists in the immediate administration of penicillin in doses of 25,000 Oxford units every three hours. Murphy, La Boccetta and Lockwood recommended that a total of 400,000 Oxford units be given in four days. Wet dressings of penicillin may be employed in strength of 400 units per 100 c c of saline solution, and penicillin may also be injected into the tissue surrounding the original lesion. Surgical incision, excision or manipulation of the primary lesion is definitely contraindicated.

**Cellulitis, Furunculosis and Carbuncles**—These lesions are also helped according to Herrell in varying degrees by the use of penicillin given intravenously or intramuscularly and applied as a wet dressing. The earlier in the course of the infection that the administration of the penicillin is started, the better the results. Likewise, with the use of penicillin, surgical incision of these infections is seldom necessary and injection of penicillin into the inflamed area is not advisable.

**Erysipelas and Erysipeloid**—The low-grade migrating forms of erysipeloid that gradually extend until, in some cases, they will involve the entire skin surface over a period of several months, respond rapidly to penicillin given by the intramuscular or intravenous route. The dose found to be effective has been 100,000 units given intramuscularly every three hours until the involution occurs.

The same results have been observed in the majority of patients with the acute type of erysipelas treated with penicillin in the manner described.

**Impetigo Contagiosa**—Roxburgh, Christie and Roxburgh have reported the successful use of penicillin as an ointment for the treatment of impetigo contagiosa and infantile impetigo, which frequently are difficult to eliminate from a nursery. They recommended the use of an ointment containing 400 Oxford units of penicillin per gram of lanette wax and petrolatum.

**Infection Due to Burns**—Likewise, the reports in the literature indicate that the secondary infection of burns of the skin may be controlled or prevented by the use of penicillin both as a wet dressing or given systemically by either the intravenous or intramuscular route.

#### REFERENCES

- 1 Herrell, W. E. Personal communication to the author.
- 2 Murphy, F. D., La Boccetta, A. C. and Lockwood, J. S. Treatment of human anthrax with penicillin, report of three cases. *JAMA* 126:948-950 (Dec 9) 1944.
- 3 Roxburgh, I. A., Christie, R. V. and Roxburgh, A. C. Penicillin in treatment of certain diseases of the skin. *Brit. M. J.* 1:524-528 (Apr 15) 1944.

# NONSURGICAL EMERGENCIES IN CASES OF THORACIC DISEASE

HERMAN J MOERSCH

THE thorax is heir to many diseases, most of which, under certain circumstances, may necessitate immediate medical attention. It is not always possible to state with certainty what comprises a true medical emergency as distinguished from a surgical emergency, or at what point one blends into the other. With this realization in mind, an attempt will be made to consider primarily the emergency conditions which generally are treated medically.

## HEMOPTYSIS

To the patient who suddenly expectorates blood for the first time, the experience is indeed alarming and looked upon as very much of an emergency. Hemoptysis also should be viewed by the attending physician as an emergency, at least until its cause has been adequately determined. Of the more common causes of hemoptysis, I shall consider tuberculosis, acute edema of the lung, pulmonary embolism, pneumonia, bronchiectasis, pulmonary abscess, broncholithiasis, carcinoma of the lung, adenoma of a bronchus, and idiopathic bleeding.

**Tuberculosis**—Tuberculosis is the most frequent cause of hemoptysis, and bleeding may be the first warning of this disease. It is estimated that in approximately a third of all cases of pulmonary tuberculosis hemorrhage occurs before the diagnosis is made. The initial hemorrhage is seldom fatal. It has been estimated that hemorrhage probably occurs in two-thirds of all cases of pulmonary tuberculosis at some time during the course of the disease. Men are somewhat more prone to bleed than women. One is not justified in making a diagnosis of pulmonary tuberculosis on the basis of hemorrhage alone. There must be other supporting evidence of the disease such as definite roentgenologic signs or the demonstration of *Microbacterium tuberculosis* in the sputum. The importance of early and prompt diagnosis of pulmonary tuberculosis is self-evident, and hemoptysis due to this disease truly constitutes an emergency until proper and adequate treatment is started. The treatment of pulmonary tuberculosis has been so well established that further consideration of the disease is not warranted at this time.

**Acute Edema of the Lung**—Acute edema of the lung comprises one of the most dramatic as well as terrifying of the pulmonary emergencies that must be treated medically. Expectoration of bloody sputum is often one of the most prominent symptoms. The patient may or may not expectorate copious amounts of sputum. The sputum is generally thin and watery, often frothy in consistency and pinkish in color. The patient's breathing is generally labored, noisy and bubbling.

in character, and is aptly designated by the term "death rattle." The patient's face and extremities are generally dusky in color and the superficial veins of the face, neck and upper extremities may be distended. As the condition progresses, the extremities become cold and blotchy purple in color. Percussion of the thorax usually reveals increased dullness over the posterior portions of both lower lobes. On auscultation, coarse, bubbling râles are found scattered over the entire thorax and are most audible over the trachea. As fluid accumulates in the pleural cavity, the breath sounds disappear at the base of the lungs.

The patient's condition is usually so critical that it is often impossible to obtain a satisfactory roentgenogram of the thorax. If it is obtainable, it may present a varied picture, usually resembling an extensive patchy infiltration with greatest density at the bases and in the hilar regions. It often reveals large, more or less circumscribed areas of increased density, which may occupy a considerable portion of the pulmonary fields. There also may be evidence of pleural effusion.

Any suppurative pulmonary disease in which there is an abundance of sputum may produce a clinical picture which simulates that of acute edema of the lung. Care must be exercised to distinguish the two conditions as the treatment to be employed varies greatly. The past history and the character of the sputum are of considerable importance in the differential diagnosis. If the sputum is purulent in character, the lesion is more likely to be inflammatory in nature. It must be remembered, however, that pulmonary edema may develop secondary to suppurative pulmonary disease, and when this occurs it may be impossible to state where one condition leaves off and the other begins.

Acute edema of the lung may be due to many factors. Anything that causes a failure of the left ventricle will bring about such a state. A common cause is the intravenous administration of excessive quantities of fluid, especially in the presence of acute renal failure and in cases in which the serum protein has been depleted. It may occur as a result of any condition that gives rise to an increased pulmonary capillary permeability, such as an acute infectious process. It also may result from chemical irritation or severe anoxemia.

Early and prompt treatment is imperative if the patient with acute pulmonary edema is to survive. Oxygen therapy is the most important treatment available for incipient or actual pulmonary edema. It should be used promptly and not withheld until cyanosis occurs. Oxygen is best administered by means of a mask, when it is administered in this manner, its concentration can be more adequately controlled and it may be given in higher concentrations than is possible when an oxygen tent is used. It may at times be of value to combine the oxygen with helium. Barach, Martin and Eckman have pointed out that, theoretically, it should be of value to administer oxygen with positive pres-

sure. Although this may be of some value in certain selected cases, thus far no completely satisfactory apparatus is available for the administration of oxygen in this manner. Venesection often may be of value in cases of acute edema of the lung. Diuretics such as anurophaline, given intravenously may be of help.

**Pulmonary Embolism**—Pulmonary embolism is one of the most serious of medical as well as surgical emergencies. Although hemoptysis occurs in pulmonary embolism it is usually one of the later manifestations. There are certain conditions which seem to predispose to embolism. Among these may be mentioned operations especially those for malignant lesions. It is most common among patients who are obese, among those suffering of heart disease, and among those who are more than forty years of age.

There is very little to do for a massive pulmonary embolism. As a matter of fact, the patient generally has died before aid can be summoned. A great deal, however, can be done in the prevention of pulmonary embolism and in the care of the patient who has had a nonfatal pulmonary embolism. Prompt recognition of a nonfatal embolism is imperative, for the victim is in grave jeopardy, for a time of a recurrent and even fatal attack. A careful clinical history is of the greatest importance in the diagnosis of pulmonary embolism. Large pulmonary emboli usually are accompanied by sudden severe pain throughout the thorax. The pain is associated with dyspnea, severe weakness and a sense of impending death. The patient usually is drenched in cold perspiration and has a rapid and often imperceptible pulse, a lowered blood pressure and an ashen color and often appears in shock. Smaller emboli may give rise to a very similar picture, but more often this classic picture is lacking. Pleurisy, especially if associated with dyspnea occurring in the postoperative period, should cause one to suspect the possibility of embolism. Hemoptysis occasionally may be the first manifestation of embolism. Often the only inkling of a small embolus may be a sense of apprehension and anxiety associated with palpitation and dyspnea. Unexplained fever in the postoperative period may be the only warning of such an accident. Vines found in his study of postmortem material, that in 15 per cent of cases of pulmonary infarctions there had not been any clinical symptoms.

The physical findings in cases of pulmonary embolism are dependent on the site and size of the embolus. If the embolus has occurred close to the surface of the lung, there may be dullness to percussion and a pleural rub may be heard over the consolidated portion of the lung. The roentgenographic findings are only occasionally indicative of embolism and are extremely variable and best described as a unilateral chronic passive congestion with accentuation of the hilar shadow when compared with the findings on the other side. Electrocardiography often may yield highly significant findings which are suggestive of embolism, as has been pointed out by White and Barnes.

Much can be accomplished in the prevention of pulmonary embolism by constantly keeping in mind the prevention of stagnation of circulation. When pulmonary embolism has occurred and the patient has survived the initial shock, a great deal can be done in the care and prevention of further emboli. Barker has recommended the immediate intravenous administration of  $\frac{1}{2}$  grain (0.032 gm) of papaverine and  $\frac{1}{100}$  grain (0.00065 gm) of atropine to combat the tendency of reflex constriction of the pulmonary vessels. Barker, Allen and Waugh have demonstrated that dicumarol is of great value in preventing pulmonary embolism and Barker has considered its administration elsewhere in this number. Dicumarol requires twenty-four to thirty-six hours to exert its beneficial effect, should an immediate anticoagulating effect be required, heparin can be administered intravenously until the dicumarol has had an opportunity to take effect. It is important that the coagulating time of the blood be closely watched and kept at between fifteen and twenty minutes while heparin is being administered.

**Pneumonia**—Since the advent of chemotherapy in the treatment of pneumonia, this disease has come to be looked upon as much less of an emergency than it has in the past. It must, however, be classed as one of the most important of the medical pulmonary emergencies. Expectoration of blood is often one of the cardinal symptoms of pneumonia and may be the first sign to attract the attention of the patient and the physician to the fact that a serious pulmonary disease exists. Early and prompt diagnosis still remains an important factor in the successful treatment of this disease. The possibility of pneumonia must always be considered in any case in which fever, general malaise and coughing are present. It must be remembered that pneumonic processes situated centrally within the lung may present few physical findings and often cannot be demonstrated except on roentgenologic examination. Although bacteriologic studies are of value in the study of pneumonia, since the advent of chemotherapy they are not as essential as they formerly were.

Chemotherapy is the procedure of choice in the treatment of pneumococcic pneumonia, and in other types of pneumonia it should be given an adequate trial. Among the most generally used chemotherapeutic and antibacterial agents are sulfadiazine, sulfathiazole, sulfamerazine and penicillin. Pneumonia of the virus type does not, as a rule, respond to chemotherapy. When any reasonable doubt exists as to the type of pneumonia, chemotherapy is indicated. The method of administration, dose and precautions involved have been so thoroughly and completely considered in the literature that they will not be repeated here. It should, however, be pointed out that adequate nursing care and the use of oxygen, where indicated, are still valuable adjuncts in the successful treatment of pneumonia.

**Bronchiectasis**—One of the most common causes for recurrent hem-

optysis is bronchiectasis. The initial hemorrhage may be very alarming to the patient until the true underlying cause is established. As a rule, the amount of blood expectorated in cases of bronchiectasis is small and bleeding is likely to occur after overexertion. Occasionally, the volume of blood expectorated may be very large and immediate medical attention may be required. At times, the purulent secretions associated with bronchiectasis fail to drain properly and this gives rise to a clinical picture that closely simulates that of pulmonary abscess or pneumonitis. As a rule, attacks of chills and fever associated with retained secretion are self-limited, but other medical measures such as the use of chemotherapeutic agents or bronchoscopic aspirations of the dammed-back secretions occasionally may be required for relief. The possibility of a metastatic abscess of the brain secondary to bronchiectasis must always be kept in mind.

The diagnosis of bronchiectasis usually can be made readily from the history of a chronic cough, the typical character of the sputum, which generally can be produced by inversion of the patient, and from the presence of clubbed fingers and positive roentgenographic evidence of the disease. On physical examination, coarse rales generally can be heard over the site of involvement. At times difficulty may be experienced in distinguishing bronchiectasis from such lesions as tuberculosis, pulmonary abscess, benign and malignant lesions of the bronchi, foreign bodies, pulmonary stones and other pulmonary lesions. This is in part due to the fact that bronchiectasis frequently accompanies such lesions. Whenever there is any question as to the diagnosis or whenever surgical treatment is contemplated, bronchoscopic studies and bronchograms should always be employed, as this is the only method to determine the exact extent and type of involvement.

Early and prompt diagnosis is important in the successful treatment of bronchiectasis. When the disease is limited to one lobe, especially if the patient is young, the lobe can be removed surgically with very little risk and with excellent results. The more extensive the involvement and the older the patient, the greater is the surgical risk and the poorer are the postoperative results. If the disease is very extensive and unsuitable for surgical treatment, postural drainage, avoidance of colds and overexertion, and removal of foci of infection are advisable, and administration of penicillin, by means of a nebulizer or other chemotherapeutic agent, is worthy of consideration.

**Pulmonary Abscess.**—Pulmonary abscess should always be looked on as a medical emergency as prompt treatment is important. In cases in which a pulmonary abscess is neglected, the mortality rate is extremely high. It is well to recall that the onset of abscess of the lung may be as insidious as that of tuberculosis. Hemorrhage may be a prominent and dramatic symptom. Although the diagnosis of pulmonary abscess usually can be made from the history, physical findings and roentgenographic findings, it often is extremely difficult to distinguish this disease

from other types of suppurative disease of the lung. The etiologic factors involved in the development of pulmonary abscess are numerous indeed. In my experience, abscesses of the lung have been about equally divided between those that follow surgical procedures and those that do not. Tonsillectomy performed with general anesthesia and pneumonia have been the most frequent etiologic factors. Bronchoscopy and bronchography are often of great value in the differential diagnosis. Many pulmonary abscesses will clear up spontaneously under adequate rest in bed, but, as a rule, bronchoscopic aspiration or surgical drainage will be found necessary. The most important factor in the successful treatment of abscess of the lung is its early and prompt recognition.

**Broncholithiasis**—The erosion of a calcareous lymph node into the tracheobronchial tree may give rise to alarming pulmonary symptoms, including hemoptysis. The symptoms of broncholithiasis are dependent on the size and shape of the calculus and the degree and duration of bronchial obstruction. The extension of the calculus into the tracheobronchial tree is generally manifested by a sudden, severe, paroxysmal cough, usually associated with thoracic oppression, substernal constriction or a severe tearing sensation. The cough may be accompanied by a so-called asthmatoïd wheeze, to which the term "stone asthma" has been applied. At times, the symptoms are not as dramatic and consist of attacks of chills, fever, recurrent pneumonitis, malaise and loss of weight. Unless the patient has expectorated a piece of calcareous material, the clinical history and physical examination are of little value in arriving at a correct diagnosis. Roentgenographic demonstration of calcified material in the tracheobronchial tree is of considerable aid in suggesting a correct diagnosis. Bronchoscopic visualization of the calculus or calculi, or the expectoration of such material is essential for a positive diagnosis. Broncholiths should be removed as soon as possible, for if they are allowed to remain they may lead to serious sequelae. This was well illustrated in a case of broncholithiasis that recently came under my observation. Bronchiectasis and a metastatic abscess of the brain developed and the patient died. Broncholiths are best removed bronchoscopically.

**Carcinoma of the Lung**—Carcinoma of the lung properly should be classified as a surgical rather than a medical emergency. Inasmuch as early diagnosis is paramount for successful treatment and since the symptoms of carcinoma of the lung closely simulate those of other inflammatory diseases of the lung it is essentially the physician who must discover its presence. Hemoptysis is a common and often an initial symptom of the disease. In my experience, approximately half of the patients with carcinoma of the lung will expectorate blood and the amount of blood expectorated varies considerably. It is not uncommon for the clinical history of carcinoma of the lung to simulate that of pneumonia, and the expectoration of blood may be regarded as part

of the pneumonic process. In half of the cases of carcinoma of the lung that have been observed at the Clinic, a diagnosis of pneumonia had been made at some time during the course of the disease. The possibility of carcinoma of the lung must always be considered in any case in which a patch of so-called pneumonia does not clear up within three weeks. The cardinal symptoms of carcinoma of the lung are cough, hemoptysis, expectoration and recurrent attacks of fever. The most significant physical findings are lagging of the involved side of the thorax and suppression of breath sounds. The roentgenographic findings are of considerable value. Bronchoscopy probably offers the most valuable aid in arriving at an early and accurate diagnosis.

**Adenoma of a Bronchus**—Recurrent attacks of hemoptysis, usually of some intensity, occurring in a case in which the patient is less than forty years of age, either with or without associated physical or roentgenographic findings, should cause one to suspect the possibility of adenoma of a bronchus. Adenoma of a bronchus, if uncomplicated, usually can be treated successfully either bronchoscopically or by operation without a high degree of risk.

**Idiopathic Bleeding**—A group of patients consults a physician because of pulmonary hemorrhage, sometimes of severe degree, for which no adequate explanation is apparent. The clinical history and the results of physical examination and of roentgenologic and laboratory examination are to all purposes negative. There is no evidence to suggest a blood dyscrasia or vitamin deficiency. On bronchoscopic examination no organic lesion can be found but it will be detected that the least manipulation of the bronchial mucosa is followed by the oozing of blood. As a rule, curettage of the bronchial mucosa followed by the insufflation of sulfanilamide or one of its derivatives usually will cause a subsidence of bleeding. The factors involved in the production and relief of this condition are not clearly understood.

#### DYSPNEA

A large number of patients have sudden and often severe attacks of dyspnea of pulmonary origin and this condition must be looked upon as a true medical emergency. Among the more common pulmonary disturbances that cause such dyspnea I shall consider asthma, pneumothorax, massive atelectasis, cystic disease of the lung and pleurisy.

**Asthma**—The most frequent pulmonary cause of acute dyspnea is asthma. An acute severe attack of asthma, "status asthmaticus," truly represents a medical emergency. At the time of the acute attack it may not be possible or wise to attempt a complete investigation of allergens, but attention must be directed to the immediate relief of the patient. If there is obvious evidence of the presence of an allergic factor it should be eliminated promptly. Various agents are available in dealing with acute asthma.

Epinephrine administered hypodermically remains one of the most



useful aids in relieving acute asthma. A dose of 7 minims (0.46 c c) of solution of epinephrine hydrochloride is usually administered. This dose may be repeated as often as required. Epinephrine also may be administered as a spray or in oil, but when the drug is administered in this manner the dose is more difficult to gauge than it is when a solution of epinephrine is administered hypodermically. Aminophylline and ephedrine also have proved of great value in relaxing bronchial spasm. In cases of acute and severe asthma, the administration of oxygen or of oxygen in combination with helium may afford a great deal of relief.

**Pneumothorax**—Spontaneous pneumothorax is a cause of sudden acute dyspnea. The degree of dyspnea is dependent in part upon the degree of collapse of the lung. Patients may have complete collapse of one lung with no appreciable dyspnea, while at times a partial collapse will cause considerable distress. Bilateral complete collapse of the lungs produces severe dyspnea and will terminate fatally if not promptly relieved. Pain over the affected lung is usually an early symptom and varies considerably in character and degree. The pain may be referred to the abdomen or shoulder and may simulate the distress produced by an acute abdominal disease. Cough may or may not be present, if present, it is usually nonproductive. There may be a slight elevation of the temperature and a slight increase in the pulse rate. Classically, the physical findings should consist of absence of tactile fremitus and diminution or absence of voice and breath sounds over the involved side. Lagging respiration on the affected side frequently can be detected. A positive coin test is of value. All too frequently, even when a patient may be known to have a pneumothorax, it may be impossible to establish the side of involvement on the basis of the physical findings alone. Roentgenologic examination of the thorax is the most valuable method of diagnosis.

In most cases of pneumothorax, the condition will clear up without treatment other than rest in bed. If the pneumothorax is due to tuberculosis, treatment should be directed to this end. Moorman recommended converting the spontaneous pneumothorax into an artificial pneumothorax for relief of pain, and if the condition should accidentally be due to tuberculosis this would constitute good treatment. He also expressed the opinion that this procedure tends to aid in the formation of adhesions so that the pneumothorax will be less likely to recur.

If pneumothorax is associated with severe dyspnea, the use of oxygen may be of value. As a rule, it is necessary to use the oxygen for only a few days, for the patient tends to adjust himself rapidly to the pneumothorax. In case of bilateral pneumothorax or tension pneumothorax, immediate aspiration of air from the pleural cavities in addition to oxygen therapy may be necessary.

**Massive Atelectasis**—One of the most dramatic lesions of the lung

that may be classified as a medical emergency is massive atelectasis. This occurs as the result of obstruction of a bronchus, usually by a mucous plug. It is especially prone to occur after operations have been performed on the thorax and abdomen or after trauma. It is more likely to occur in cases in which patients have a low-grade infection of the upper part of the respiratory tract or have a tenacious type of nasopharyngeal secretion.

Massive atelectasis of the lungs manifests itself by dyspnea and cyanosis. Respiration rapidly becomes labored and is associated with a hacking cough, and the patient experiences difficulty in raising secretions. There is an elevation of temperature with an increase in the pulse rate. The patient may complain of a sense of tightness in the involved side of the thorax.

The physical findings in cases of massive atelectasis are usually very striking. There is a sudden respiratory lag on the involved side of the thorax. The apex beat will be shifted toward the side of involvement. Percussion will reveal dullness over the atelectatic area and the breath sounds will be decreased in intensity. Roentgenograms of the thorax are of great value in making the diagnosis. An opacity of the lung will be noted over the involved side, with elevation of the diaphragm, while the mediastinum will be found shifted toward the involved side.

The treatment of massive atelectasis is relatively simple and efficacious. Frequently the patient can be encouraged to cough effectively. If the patient who has undergone an operation can do this by holding the site of the operation firmly, he may expectorate the obstructing bronchial plug. The same thing can at times be accomplished by change of position. Hyperventilation of the lung with carbon dioxide and oxygen and deep breathing exercises will frequently suffice. If prompt relief is not obtained by these methods, bronchial catheterization or better, bronchoscopic aspiration of the secretions obstructing the bronchus will be followed by immediate improvement in the patient's condition and by prompt changes in the physical and roentgen findings. The earlier atelectasis is recognized and proper treatment instituted, the less danger there is of the development of secondary pulmonary complications. Chemotherapeutic agents should always be employed promptly when indicated.

**Cystic Disease of the Lung**—Recurrent attacks of severe dyspnea with cyanosis, nonproductive cough and asthmatic attacks, particularly in cases in which the patients are infants or children, should cause one to suspect the presence of cystic degeneration of the lung. In the case of older patients, progressive dyspnea with or without preceding respiratory infection warrants the same suspicion. The attacks of acute dyspnea are caused by a sudden trapping of air in the cyst owing to a check valve mechanism between the cyst and the bronchus. If there is free communication between the cyst and the bronchus or no communication at all, such attacks do not occur. The symptoms as might

be anticipated, may be fluctuating and progressive and may closely simulate those of spontaneous pneumothorax. The diagnosis is dependent primarily on the roentgenologic findings. In cases of cystic disease, as a rule, in contrast to pneumothorax, the pulmonary tissue contiguous to the cyst usually will be compressed downward and toward the base of the lung. In cases of pneumothorax, it is more likely to be compressed toward the root of the lung. Bronchography may be of value in the differential diagnosis. Artificial pneumothorax may at times be required to distinguish a cystic lesion from pneumothorax or emphysema. If the cyst should contain fluid, difficulty may be experienced in distinguishing it from tumor, abscess and localized empyema. If the pulmonary symptoms become acute as a result of the trapping of air, it may be necessary to aspirate the air as a lifesaving procedure. Lobectomy is the procedure of choice in cases in which the symptoms warrant it.

**Pleurisy and Pleural Effusion**—The patient suffering from an attack of pleurisy may experience pain of such severity that immediate attention becomes imperative. Care must be exercised to distinguish the pain of pleurisy from pain in the thoracic wall and pain due to diseases of the central nervous system or spinal column. Diaphragmatic pleurisy especially may offer difficulty in differential diagnosis.

A characteristic sign of dry pleurisy is the pleuritic friction sound, which is heard either as a fine rub or coarse leather creaking. The friction rub also is usually palpable. Usually, the friction and pain are increased by deep respiration. Roentgenologic examination is of very little value in diagnosis of pleurisy, although it is of considerable value in the determination of its cause.

The treatment of pleurisy varies with its severity. Frequently, local pressure over the thorax is all that may be required. The local application of heat in any form is often of benefit. The use of codeine may be necessary to control coughing, which may aggravate the pain. In severe pleurisy that is not controlled by the methods outlined, the blocking, with procaine hydrochloride, of the nerves of the skin overlying the site of pain will generally afford immediate relief.

Pleural effusion, which may or may not be an accompaniment of dry pleurisy, may often become so severe that dyspnea becomes very pronounced and immediate aspiration of fluid is necessary for relief. Careful study of the aspirated fluid is of considerable value in the determination of the cause. It is of interest that, if pleural effusion that is due to cardiac disease or that follows surgical procedures is excluded, if the pleural effusion is found to be bloody in character there is better than a 90 per cent chance that the effusion is due to carcinoma. If the effusion is purulent in character, it may be successfully treated by instillations of penicillin and by surgical drainage in cases in which treatment with penicillin does not prove successful.

## OTHER CONDITIONS

There are numerous other conditions, such as aspirated foreign bodies, mediastinal tumors, mitral stenosis, aortic aneurysm and diaphragmatic hernia, which may constitute a medical emergency but they are generally classified as surgical or vascular in type. These will not be discussed at this time.

It becomes readily apparent that the thorax, as the abdomen, is the site of many acute diseases and that early treatment is of paramount importance.

## REFERENCES

- 1 Barach, A. L., Martin, John and Eckman, Morris. Positive pressure respiration and its application to the treatment of acute pulmonary edema. *Ann. Int. Med.* 12 754-795 (Dec.) 1938.
- 2 Barker, N. W. The use of dicumarol in surgery. *Minnesota Med.* 27 102-106 (Feb.) 1944.
- 3 Barker, N. W., Allen, E. V. and Waugh, J. M. The use of dicumarol [3,3-methylenebis (4-hydroxycoumarin)] in the prevention of postoperative thrombophlebitis and pulmonary embolism. *Proc. Staff Meet., Mayo Clin.* 18 102-107 (Apr. 7) 1943.
- 4 Barnes, A. R. Pulmonary embolism. *J.A.M.A.* 109 1347-1352 (Oct. 23) 1937.
- 5 Moorman, J. F. Spontaneous pneumothorax in apparently healthy young adults. *J. Oklahoma M. A.* 36 277-281 (July) 1943.
- 6 Vines, R. W. Pulmonary infarction: a clinical and pathological study. Thesis, University of Minnesota 1943.
- 7 White, P. D. Pulmonary embolism and heart disease: a review of 20 years of personal experience. *Am. J. M. Sc.* 200 577-581 (Nov.) 1940.

# NONSURGICAL EMERGENCIES IN OBSTETRICS

JOHN E. FABER

THE obstetrician perhaps more than any other medical specialist requires special training and equipment to cope with the emergencies that occur constantly in his practice. Most of these emergencies can be managed on a medical basis.

In the field of obstetrics most deaths can be classified as attributable to three causes, as follows: (1) toxemia, (2) hemorrhage and (3) infection. Prenatal care and the use of chemotherapy and penicillin in the last decade have effected a marked reduction in mortality in the first and third groups but the mortality in the second group remains high. It is earnestly hoped that within the next few years increasing knowledge concerning transfusion of whole blood and plasma and their substitutes also may effect a major reduction of mortality due to hemorrhage.

There are, of course, emergencies due to conditions other than toxemia, hemorrhage and infection but since they account for a negligible portion of deaths in the field of obstetrics and since space is limited, they will not be discussed here. Consequently, I will outline the differential diagnosis and the routine management of only medical emergencies attributable to the three previously mentioned causes.

## TOXEMIA

Toxemia may occur either early or late in pregnancy. Pernicious vomiting and chronic hypertension are evident early. Late toxemia is usually classified as convulsive or nonconvulsive in type.

**Pernicious Vomiting**—Although the etiology of pernicious vomiting of pregnancy is obscure, most authors classify the condition with toxemia. It has its inception in the first trimester, often shortly after the beginning of amenorrhea. In its milder form, the symptoms are anorexia, nausea and vomiting.

In the majority of cases of pernicious vomiting, which occurs in varying degrees of severity in about a third of all pregnant women, the symptoms can be controlled by adherence to a rigid regimen of dietary management consisting of small, dry feedings at four-hour intervals. The food should be high in carbohydrate value and bland in nature. Vitamin supplements, particularly those in the B group, are valuable since such a diet is usually deficient in vitamins. Fluids should be taken liberally between feedings. Often carbonated drinks are more readily tolerated than other fluids. Freedom from worry and household responsibilities and a rest period several times a day are advisable. Some mild sedative, such as phenobarbital or a bromide, may be used.

in sufficient amounts to effect relaxation. Treatment is much more effective when the patient is in the hospital.

If vomiting persists in spite of this management, severe hyperemesis may develop. Signs and symptoms of dehydration, hemoconcentration and vitamin deficiency are present. There is pallor, dry skin, salivation and rapid loss of weight and, as the condition progresses, there is often a rising pulse rate, slight fever and oliguria. Blood studies may show leukocytosis due to hemoconcentration with a low concentration of blood chlorides.

In severe cases of pernicious vomiting, jaundice, visual disturbances and polycuritis may occur. These are grave complications and demand immediate treatment in the hospital. This provides an opportunity for enforcing complete bed rest and close observation and also facilitates laboratory studies. Treatment is directed toward combating dehydration, avitaminosis and acidosis. In the acutely ill patient this is probably best accomplished by means of intravenous infusions of 10 per cent glucose in physiologic saline solution. Of late years it has been our practice at the Clinic to fortify these solutions with injectable vitamin concentrates. Since a high carbohydrate intake further increases the demand for certain vitamins in the B group, particularly thiamine, the use of intravenous glucose might even enhance an impending deficiency state if vitamins were not supplied in adequate amounts. During the initial period of hospitalization it is often advantageous to discontinue the oral intake of all foods and fluids until the tendency toward vomiting actually has ceased. As previously mentioned, adequate fluid can be supplied by the intravenous route, or in some patients, by the rectal route, utilizing a solution of 5 per cent glucose or even by the subcutaneous route utilizing the continuous drip method. Sufficient sedation to keep the patient relaxed and slightly drowsy is beneficial. For this purpose, hypodermic injections of phenobarbital sodium, 2 grains (0.13 gm), are effective.

After the nausea has been controlled, frequent small, dry feedings of bland foods again may be instituted and with improvement in the patient's condition, the diet may be increased in caloric content and volume in accordance with the patient's tolerance. Sedatives can then be given orally.

Several years ago reports appeared in the literature regarding the use of pyridoxine in the treatment of hyperemesis. This preparation has been used at the Clinic in both mild and severe cases of pernicious vomiting in doses of 50 mg intravenously every one to three days, and in many cases the results apparently have been good. The frequency of its administration appears to vary considerably and we have relied largely on the patient's subjective symptoms and improvement in regulating the injections.

Therapeutic abortion for hyperemesis is rarely, if ever, a necessary part of treatment, since medical treatment including the use of in-

travenous glucose almost always maintains the patient in good condition until the process is corrected

**Chronic Hypertension**—Since chronic hypertension of itself is seldom an emergency condition unless it is complicated by some other disease, it will not be discussed in detail in this paper. This condition manifests itself by albuminuria and elevation of blood pressure. It antedates the pregnancy and therefore is evident on the first prenatal examination.

**Preeclampsia**—In its incipient form preeclampsia often is first recognized by a slight rise of blood pressure at the time of prenatal examination. It occurs in late pregnancy. A significant rise of the diastolic blood pressure is regarded by many physicians as a warning sign. It should be emphasized that a jump of twenty points in the blood pressure of a patient who previously had a low pressure is as significant as a similar change in a case in which the pressure was near the upper limits of so-called normal.

There may be rapid gain in weight, albuminuria and edema. Sometimes the first symptom is edema. If some edema occurs early in the course of pregnancy, toxemia is more likely to develop later than if edema is not present. Sudden increases in body weight are suggestive of fluid retention.

Rises in the level of serum sulfate often presage the onset of toxemia. At the Clinic this test is considered the most valuable of all blood chemistry determinations in cases of suspected preeclampsia. Ophthalmoscopic examination often reveals narrowing of the retinal arterioles of a spastic nature.

Patients who have evidences of incipient toxemia must be observed more closely than the average patient because of the possibility of progression of the process. Usually the patient may be up and about but rest periods in the morning and afternoon and limitation of activities are advisable.

Usually the use of some sedation in the form of a barbiturate, such as phenobarbital,  $\frac{1}{2}$  to  $1\frac{1}{2}$  grains (0.032 to 0.1 gm), three times a day, is instituted. The diet should be bland and low in carbohydrate value with optimal amounts of protein daily. The sodium ion should be eliminated from the diet as far as possible and the use of salt or baking soda should be avoided. In addition, 1,500 to 2,000 cc of fluids daily should be taken. If there is any edema that does not subside quickly on this management, ammonium nitrate or ammonium chloride in doses of 90 grains (6 gm) may be given. In a considerable number of cases at the Clinic the edema has subsided on this management, the blood pressure has lowered decidedly or at least remained stationary and the patient has been carried along to term and the spontaneous onset of labor.

If incipient toxemia does not respond satisfactorily or if the toxemia when first noted is severe, the patient should be hospitalized so that she can be watched closely and kept at complete rest in bed. The

presence of such subjective symptoms as persistent headaches, vertigo and nervous irritability often indicate that the patient should be observed in the hospital where a salt-free diet can be more closely administered. The intake of protein is kept at about 60 gm daily and fluids are given liberally. Ammonium nitrate, in the previously mentioned amount is continued and sedation is given to the point of effecting relaxation. The blood pressure is checked every two to four hours and the urine is examined daily to determine the degree of albuminuria. The daily weight, the twenty-four hour intake and output of fluid are recorded. If some improvement, such as decline in blood pressure, increase of urinary output to exceed the fluid intake and loss of weight and alleviation of subjective symptoms is evident, management can be continued status quo, until the fetus is viable. Regular ophthalmoscopic examination of the fundal vessels is also a valuable diagnostic aid in determining the patient's progress.

Since the likelihood of permanent vascular and renal damage increases in direct proportion to the duration of toxemia, one hesitates to carry such patients much past the time when induction of labor becomes feasible even though the toxemia may be under satisfactory control. If satisfactory progress is not made on the outlined regimen, the intravenous injection of glucose solutions is advisable. If 500 cc of a 10 per cent solution is not effective in producing diuresis, a 20 or even a 30 per cent solution can be used in smaller volume. The injections may be given two or three times daily.

If the progress of the patient is fairly satisfactory an effort should be made to carry her along until the period when the fetus might be viable and not too premature. The decision as to how long the pregnancy should be allowed to continue must be based on the understanding that prolonged toxemia increases the likelihood of permanent vascular damage. On the other hand, in view of our present knowledge concerning care of the premature infant, it is far better to have a premature baby than one dead or irreparably damaged by the effects of toxemia. Hence, management of this problem necessitates fine judgment, taking into consideration these factors plus the parity of the patient.

If in spite of treatment the toxemia becomes worse, this development often is manifested by an increase of headache, visual disturbances and sometimes epigastric pain. There is also a diminution of urinary excretion with increasing amounts of albumin. The values for serum sulfate and uric acid of the blood increase. The blood urea also may be slightly elevated. Twitching of the muscles and increased nervous irritability often are present and must be regarded as grave signs possibly indicating the approach of convulsions. Sedation with morphine sulfate,  $\frac{1}{4}$  grain (0.016 gm) every four to six hours, then is indicated but care must be taken not to depress the respirations to less than eleven or twelve per minute.



Interruption of pregnancy is indicated if treatment is without results. The election of method for this procedure is largely dependent on the circumstances. In the case of a multiparous woman rupture of the membranes under aseptic precautions usually will suffice. In the case of a primipara with the cervix well effaced and the presenting part well engaged, this again may be the procedure of choice. If the cervix is not well effaced, the onset of labor may be hastened by the utilization of a large size Voorhees bag. The severe degree of morbidity often ascribed to this procedure has not been encountered at the Clinic and we still employ it on occasions. A simple expedient, one which possibly is not employed frequently enough in the type of case in which use of a bag is undesirable, is a Willett forceps. In the case of a primipara, with a high riding presenting part and a long, uneffaced cervix, it may be evident that the medical measures described previously for the induction of labor may consume a long time before delivery actually can be effected. In such cases and in those of cephalopelvic disproportion, cesarean section is the treatment of choice. However, it is well to recall that the patient is desperately ill and that a major surgical procedure carries with it a considerably increased risk.

**Eclampsia.**—The institution of prenatal care has led in general to early recognition, diagnosis and treatment of toxemia. As mentioned previously, if the condition cannot be controlled pregnancy can be interrupted before convulsions supervene. An occasional case is still encountered, however, in which the patient has not availed herself of prenatal care or in which, in spite of such care, sudden and fulminating toxemia with convulsions develops between prenatal visits. The convulsive state may develop first in the prepartum, intrapartum or immediate postpartum period, but regardless of time of occurrence, the plan of attack must be as follows: (1) control of the convulsion, (2) protection of the patient from injury and (3) elimination of toxic products from the body before considering the necessity for delivery.

The high mortality rate (20 to 30 per cent) which attended the now discarded methods of accouchement forcé or cesarean section in cases of convulsions show the fallacy of such management. A patient who is having or has had convulsions should be placed in a quiet, darkened room that is protected as much as possible from external noises. The bed should be provided with sideboards but otherwise no effort at restraint of the patient should be made. A padded tongue blade can be inserted between the molar teeth to prevent injury to the mouth and tongue during the convulsion.

In an effort to control the convulsions, an initial dose of  $\frac{1}{4}$  grain (0.016 gm.) of morphine sulfate may be given and this may be repeated at intervals of one to four hours depending on the size of the patient and the severity of the seizure. The best guide to dosage is the respiratory rate which should not be depressed to less than 12 to 14 respirations per minute. The intravenous administration of magnesium

sulfate in 20 c.c. doses of a 10 per cent solution enhances the sedative effect of morphine by lessening nervous irritability and, in addition, stimulates the excretion of fluids from the body and thereby lessens edema. However, the amount of magnesium sulfate given must not exceed 6 gm. in twenty-four hours.

If the convulsions are not controlled by these sedative measures, a barbiturate may be given by intravenous injection. In our experience pentobarbital sodium has been satisfactory when carefully used. The inhalation methods of administering anesthetic agents should be avoided. After sedation has been effected, stimulation of diuresis and of elimination of toxins is advisable. Hypertonic solutions of glucose are efficacious, if the edema is severe, 250 c.c. of a 20 or 30 per cent solution may be utilized, but if the edema is slight, 1,000 c.c. of a 5 or 10 per cent solution may prove effective. The injections may be repeated three or four times in twenty-four hours or until diuresis is established. Improvement is evidenced by cessation of the convulsive seizures, diminution of the coma, diuresis and a warm, moist skin. After the convulsions have ceased the administration of oxygen through a nasal mask or if a mask is not available, a nasal catheter, helps considerably to counteract anoxemia. With the return of consciousness, sedation may be continued by the administration of drugs by the oral route, utilizing the barbiturates. In addition, water and fluids high in carbohydrate content, such as fruit juices, should be given by mouth, but the fluid intake must not greatly exceed the urinary output.

Fortunately a fair proportion of patients who have had convulsions go into labor spontaneously. However if this does not occur, sound medical reason dictates the initiation of labor as soon as the patient's condition has become stabilized.

### HEMORRHAGE

Hemorrhage accounts for a major portion of the reported maternal mortality, as well as a high proportion of the medical emergencies encountered in this field. Hemorrhage may be divided roughly into two groups, namely, that which occurs in early pregnancy and that which occurs in late pregnancy. Postpartum hemorrhage also will be discussed.

**Hemorrhage of Early Pregnancy**—Most hemorrhages of early pregnancy are caused by abortion, ectopic pregnancy and hydatidiform mole in that order of frequency. In addition, cervical polypi, an anomalous uterine horn and carcinoma of the cervix also are causative factors, but their occurrence is so rare that discussion of them in this article does not seem justifiable. The reader therefore, is referred to any of the well-known textbooks on obstetrics.

The differential diagnosis usually can be made on the basis of the history and physical findings. In the case of *abortion* there is a history

of coitus followed by amenorrhea or at least some disturbance of menses. The symptoms commonly associated with early pregnancy, such as nausea, vomiting and soreness and engorgement of the breasts, may be present. The bleeding, which at first may be painless and slight, usually becomes increasingly severe and is associated with crampy pain in the mid-line. In the absence of infection the pain is intermittent in character. The presence of fever indicates that the condition is complicated by infection. Examination of the pelvis reveals that the uterus is softened and enlarged, usually in proportion to the period of amenorrhea, and the cervix is soft and patulous. If bits of decidua have been expelled, the diagnosis is more certain than otherwise.

In the case of *ectopic pregnancy*, the history of amenorrhea is usually not definite. The menstrual flow may have been scanty and the usual menstrual interval may have been disturbed. The symptoms of pregnancy often are indefinite. The bleeding is almost always associated with unilateral pain that is dull, boring and constant in nature. The pain often is aggravated by physical activity, straining at stool and movements of the uterine fundus. The classical picture of ruptured ectopic pregnancy is that of sudden, excruciating abdominal pain followed by signs of shock, collapse and hemorrhage out of proportion to the amount of external bleeding. On pelvic examination the uterus is enlarged and softened and shows signs of pregnancy but often the organ is not as large as would be anticipated from the period of amenorrhea. The cervix is firm and closed. There is usually a palpable fusiform mass in the adnexal region on the side of the greater pain. If an appreciable amount of intra-abdominal bleeding has occurred, the cul-de-sac feels full and doughy and may even bulge into the vagina. Often the rectus muscle on the side of the involved tube is definitely rigid. Cullen's sign, which consists of discoloration of the skin about the umbilicus, may be present.

In the case of *hydatidiform mole* the history of pregnancy is again present and the symptoms of early pregnancy such as nausea, vomiting and headache are often more pronounced than usual. The bleeding is usually scant at first, but may later become alarmingly severe. Pain is seldom a prominent symptom. A history of passage of cystic grape-like bits of tissue makes the diagnosis of hydatidiform mole more probable, especially if the uterus is extremely boggy and is considerably larger than would be expected for the period of gestation. If the patient can be observed for a short time, unusually rapid increase in size of the uterus makes the diagnosis more certain. Because of the great increase in gonadotropin the corpus luteum enlarges and may become cystic. Enlargement in the region of either ovary is an important contributory finding in diagnosis.

In most instances, the biologic tests, such as the Friedman test, are not of great value in the diagnosis of either abortion or extra-uterine

pregnancy for, while a positive test confirms the evidence of pregnancy, a negative test only points to the fact that the chorionic villi have been nonfunctional for a week to ten days regardless of whether their implantation is intra-uterine or extra-uterine. However, in the case of hydatidiform mole the fact that the test is strongly positive even in one tenth the usual dilution of urine is of considerable diagnostic value.

**Hemorrhage of Late Pregnancy**—In the latter half of pregnancy the principal causes of hemorrhage are placenta previa, premature separation of the normally implanted placenta and, more rarely, circumvallate placenta with premature separation.

In the case of *placenta previa* the history is that of sudden onset of painless vaginal bleeding. Although the bleeding may be profuse it is seldom fatal on first occurrence. Examination of the abdomen reveals that the uterus is relaxed and soft and that the presenting part is high and usually cannot be depressed into the pelvis. The fetal heart rate may be disturbed. If the emergency is not too acute, roentgenographic study of the placenta may reveal its location.

In the case of *premature separation of the placenta* a history of trauma to the uterus may be obtained. More than half of all cases of premature separation are associated with toxemia. The amount of external bleeding is dependent on the degree of separation and in mild cases the bleeding may be painless. At first there are usually intermittent painful contractions which soon become constant. The uterus becomes rigid and boardlike and is said to feel ligneous. The fetal heart rate is rapid, and if the separation is profound the heart tones may be absent. There is often a history of fetal activity followed by no fetal movement and it may be difficult to palpate the fetal parts. As the condition progresses the signs of blood loss are out of proportion to the external bleeding.

In the case of *circumvallate placenta* bleeding is an early symptom but it is usually scant. It is improved by bed rest but tends to recur on exercise. The hemorrhage is seldom severe enough to be considered an emergency unless the condition progresses to actual premature separation of the placenta.

The diagnosis usually must be confirmed by vaginal examination under sterile precautions. Such an examination must not be attempted until preparations have been made to proceed at once with the necessary treatment. Consequently this examination will be discussed more thoroughly in a subsequent section concerning treatment.

**Postpartum Hemorrhage**—Careful observation and measurement of blood loss during the third stage of labor and during the next twelve hours are essential. The average blood loss is between 250 and 300 c.c. and when the loss is in excess of 500 c.c. the danger limit is rapidly approaching. As the bleeding becomes excessive, symptoms of shock, such as rapid pulse, falling blood pressure, sighing respiration and cold,

clammy skin, follow rapidly. The causes of excessive blood loss in the postpartum period are partial separation of the placenta, retention of a fragment of placenta or succenturiate lobe, obstetrical lacerations and failure of the uterus to contract properly and to remain contracted.

**Treatment**—In all cases of hemorrhage treatment consists of hemostasis and replacement of lost fluids and blood. Management is specifically in accordance with the diagnosis but, in general when the condition is *ruptured ectopic pregnancy*, medical management or procrastination is seldom, if ever, justifiable. The necessary surgical measures to obtain hemostasis should be begun immediately. Any attempt at blood replacement usually is futile until the operation has been begun, but sometimes measures to combat severe shock are necessary during preoperative preparation of the patient.

If a diagnosis of *hydatidiform mole* is made dilatation and curettage or even hysterotomy to control bleeding usually is the best type of treatment. Fluid loss must be replaced. Because in about 3 per cent of all cases of hydatidiform mole, chorionepithelioma develops, the patient should be observed closely. The Friedman test should be repeated at intervals for a year or more and if abnormal bleeding again should occur, dilatation and curettage and microscopic examination of the scrapings should not be delayed.

In the treatment of cases of *abortion* my associates and I have adopted a conservative attitude. The majority of patients are regarded as potentially infected. The patient is kept at bed rest in a modified Fowler's position with ice caps to the lower part of the abdomen. Replacement of blood loss is undertaken by starting intravenous administration of 5 per cent glucose in physiologic saline, a solution of acacia, blood plasma or whole blood of the correct grouping, dependent on what the need may be. An oxytocic in the form of ergonovine,  $\frac{1}{4}_{20}$  grain (0.0002 gm), is given every four hours for twenty-four hours as indicated. If bleeding is not controlled, 1 c.c. of obstetrical pituitrin (posterior pituitary extract) is injected intramuscularly. The pulse rate and blood pressure are checked at frequent intervals and the patient is observed closely for further excessive bleeding. If the patient is febrile, chemotherapy in adequate dosage is instituted. If rectal examination reveals products of conception incarcerated in the cervical os or in the vagina which cannot be expressed by bimanual pressure on the uterus, vaginal examination under sterile conditions is performed, removing the retained secundines manually or with an ovum forceps.

If hemorrhage persists in spite of these measures, curettage should be undertaken at once, utilizing a large blunt curet, or an ovum forceps. Our practice has been to conclude such a procedure by packing the uterus with a small amount of sterile gauze dusted with 5 gm. of sulfathiazole powder. The pack is allowed to remain in place from twenty-four to seventy-two hours. Bed rest is enforced until the

patient has remained afebrile for five days and the uterus is involuting satisfactorily. If infection is a complication, the period of bed rest is prolonged.

The plans for treatment of the patient who has prepartum hemorrhage usually are made at the time of vaginal examination and diagnosis. Therefore, as mentioned previously, the examination should never be attempted until all preparations have been made to proceed with whatever procedure may become necessary. In the meantime, infusions of plasma or whole blood are begun.

Treatment of *placenta previa* is dependent on the gravidity of the patient, the degree to which the placenta covers the cervical os and the patient's desire for a living infant. In all cases of central placenta previa in which there is a living child our treatment of choice is cesarean section.

In cases of incomplete placenta previa with the vertex presenting, the simplest measure is rupture of the membranes and slow release of a portion of the amniotic fluid. This is particularly applicable in the case of the multiparous woman but at times it is also effective in the primipara and is the only treatment necessary. The presenting part then descends, presses on the placenta and produces hemostasis. If this in itself does not suffice, a Willert forceps can be applied to the scalp and gentle traction applied. In selected cases in which these measures are not effective, insertion of the largest possible size hydrostatic bag has proved valuable although this increases somewhat the risk to the child. Braxton Hicks' version and bringing down one foot through the cervix so the thigh makes pressure on the placental site can be utilized when other measures fail. This is a fairly safe means of management for the mother, but the procedure is not so safe as far as the infant is concerned. It is particularly applicable if the fetus is not yet viable or is dead. Extraction should not be undertaken until the cervix has attained full dilatation. Manual dilatation of the cervix and forcible delivery have no place whatever in the management of cases of placenta previa.

In the case of *abruptio placentae* in a multipara who is near term and who has a soft dilatable cervix, medical management sometimes is satisfactory. The blood loss should be replaced and, after a sterile vaginal examination, the membranes should be stripped from about the internal os and ruptured artificially. This treatment is also applicable when the fetus is still and the separation has not become marked. However, if there is considerable separation and continued bleeding the procedure of choice is usually cesarean section. After delivery, regardless of the method used, the uterus is usually packed with several strips of iodoform gauze to prevent further loss of blood. If conservative measures do not control hemorrhage or if the uterine wall itself has been damaged by gross hemorrhage, hysterectomy becomes a necessity.

The same principles that apply in other cases of obstetric bleeding also apply to the management of *postpartum hemorrhage*. First, the cause of the hemorrhage must be accurately ascertained and corrected. A sterile vaginal examination is imperative. Vaginal lacerations or birth injuries to the cervix should be repaired. If the placenta has become partially separated and incarcerated, the uterine cavity is explored with the sterile gloved hand. The line of cleavage between placenta and uterus is found and with a sweeping motion of the hand the remainder of the placenta is separated and then extracted. Any fragments of retained placenta are removed in a similar manner. The uterine cavity is then firmly packed with sterile strips of iodoform gauze, tamponing them firmly into the fundus, cervix and apex of the vagina to insure their retention.

Oxytocics can be used in cases of atonic uterus, but if they do not rapidly produce hemostasis the uterus should be packed as previously described. Replacement of lost blood and fluids is important.

A few general statements regarding the replacement of lost fluids may be apropos. In general, replacement of fluids to a volume equal or nearly equal to the amount lost usually is desirable. This loss, as a rule, can be estimated fairly accurately. The replacement of fluids should be started early and should be rapid. Until fluids of more permanence can be obtained, infusion of saline or intravenous glucose can be started. Intravenous infusion of plasma or of a solution of acacia, which are now readily available commercially, is efficacious in combating shock.

There is, however, no really satisfactory substitute for transfusions of whole blood in the treatment of hemorrhage since there is depletion of cellular elements of the blood as well as of fluids. The blood should be of the proper group and preferably the blood of the donor and the recipient should be cross matched to avoid untoward reactions. In the light of recently acquired knowledge, determination of the Rh factor is also of importance in obstetric cases, and if any doubt about this factor exists, Rh negative blood should be used. In an effort to avoid an emergency and the resultant heavy drain of Rh negative blood from the blood bank, my associates and I have adopted the policy of obtaining an Rh determination and blood grouping on every obstetric patient at the time of admission for prenatal care. If an emergency should arise, information regarding the necessary blood type is readily available. If there is a long delay in obtaining properly grouped blood, infusions of blood plasma, which are often lifesaving, can be started. If every physician who cares for obstetric patients would obtain blood groupings and Rh determinations on six or eight healthy persons in his community who might act as donors, blood would be available in case of dire emergency and many a hemorrhaging woman might be saved who otherwise would be lost because of the delay in grouping donors.

## INFECTIONS

Although much progress has been made in the management of infection, it is still one of the three main causes of maternal death. As in any infectious process, prophylaxis is most important. Such measures as careful rectal examination only when necessary to determine progress of a patient in active labor, vaginal examination only when necessary to obtain information as to progress which is not available on rectal examination, careful masking of the examiner and aseptic preparation of the patient help to reduce the incidence of infection. An elevation of temperature after delivery should be considered evidence of infection until proof to the contrary is obtained. Such causes for fever as engorged or caked breasts, appendicitis, pyelitis, cholecystitis and acute infection of the upper respiratory tract usually can be ruled out readily.

When the diagnosis has been established the patient should be isolated from other obstetric patients, preferably apart from the obstetric pavilion. The patient should be kept at complete bed rest in a modified Fowler's position with ice bags to the lower part of the abdomen. Positive fluid balance should be maintained. If this is impossible by the oral route, intravenous infusions of 5 per cent glucose in physiologic saline can be used. In the presence of anemia, transfusions of compatible blood are invaluable. Blood cultures and blood studies, including determination of the sedimentation rate, at frequent intervals are invaluable in determining progress of the condition. Chemotherapy in adequate dosage may be begun at once. After an initial small dose to determine any unusual sensitivity to the drug, the dose should be regulated by daily determinations of blood concentration so that an optimal level of the drug may be rapidly arrived at and maintained. If progress during the first forty-eight hours is unsatisfactory, penicillin should be used particularly if bacteriologic studies indicate the presence of an organism sensitive to this medication.

Either penicillin or chemotherapy in reduced dosage should be continued for several days after the patient has become afebrile. If the distention is severe, enemas can be utilized. If the upper part of the gastro-intestinal tract is involved the institution of drainage by use of a Wangenstein or a Miller-Abbott tube is of great value and should not be long delayed. Occasional careful examination of the pelvis will determine the presence of local abscess formation and the need for surgical drainage.

In the subacute stage conventional diathermy, given either through and through or by use of a vaginal applicator, hastens improvement of the patient's condition. Bed rest should be enforced until the patient has remained afebrile for at least a week to ten days and the sedimentation rate and white blood count have dropped to near normal levels. This conservative policy of medical treatment usually results in complete recovery and often, a return of childbearing function.



## EMERGENCIES ASSOCIATED WITH THE THYMUS

ROGER L J KENNEDY AND GORDON B NEW

IN spite of the fact that proof that the thymus frequently exerts serious pressure upon the trachea is lacking and, despite the fact that the function of the thymus is still unknown, claims that it is a relatively frequent cause of alarming obstructive respiratory phenomena and of the sudden death of infants and children continue to be advanced. Proponents of these claims point chiefly to two pieces of evidence in support of their contentions: first, to the relief of symptoms that sometimes follows roentgenotherapy of the superior mediastinum, and second, to the finding of a large thymus in some infants and children who have died suddenly and unexpectedly.

These claims have been ably refuted by Morse,<sup>7</sup> Hudson,<sup>4</sup> Wilson<sup>11</sup> and other authors. The contention that some patients with stridor, dyspnea, cyanosis or other symptoms frequently improve after roentgen irradiation of the superior mediastinum does not constitute proof that they therefore suffered from enlargement of the thymus. Likewise, the finding of a large thymus at necropsy in cases in which patients have died suddenly is no proof that the thymus has been a causative factor in the death. The function of the thymus remains unknown, therefore, to invoke disturbed thymic function, a combination of disturbed thymic function and allergy or any other theory involving disturbed thymic function is unsupported by fact.

So far as the size of the thymus is concerned it should be recognized that there is considerable variation but that a thymus of considerable size is to be expected in any child who has not suffered from disease or inanition. Data published by Boyd,<sup>1, 2, 3</sup> which deal with the size of the thymus during infancy and childhood, should be more widely perused. Familiarity with these data will tend to correct some of the current misconception regarding the size of the thymus.

Throughout the years that enlarged thymus and thymic death (including status thymicolymphaticus) have been debated, able investigators and clinicians have been found supporting opposite sides of the question. Even though one may be inclined to disregard the post hoc, ergo propter hoc reasoning of some who feel that the so-called thymic syndrome and so-called thymic deaths are real entities, one cannot ignore the opinions expressed by such competent and able observers as Jackson and Bowman,<sup>5</sup> Wasson,<sup>10</sup> Pancoast<sup>8, 9</sup> and others who have expressed the opinion that they are something more than imaginary figments. However, neither they nor other proponents of the thymic syndrome and thymic death have offered proof that the thymus can exert pressure on the trachea that is sufficient to cause symptoms. The crux of the matter appears to rest on the diverse experiences of various

observers and the interpretations which they have chosen to place upon their observations. Experience at the Clinic seems uniformly to support the idea that neither concept can be supported by clinical or postmortem data.

Some years ago we<sup>6</sup> reviewed the experiences of ten years in respect to the diagnosis of chronic stridor in childhood. At that time, it was pointed out that, in some cases of stridor in which a diagnosis of enlargement of the thymus had been made, examination revealed the presence of congenital relaxation of the larynx, cerebral palsy with congenital laryngeal stridor, laryngospasm, tracheal subglottic diaphragm, tumor of the thymus or multiple papillomas of the larynx. It was pointed out at the same time that, during the period in which these patients were observed, no child with symptoms referable to hypertrophy of the thymus and no death attributable to hypertrophy of the thymus were encountered. These observations included all deaths of newborn and older infants that occurred either spontaneously or during or following anesthesia. Since this report was made, our experience has not changed.

At the present time, it appears useless to attempt to dissuade the proponents of the theories of enlarged thymus and thymic death from expounding their beliefs before the medical profession and the laity. However, those physicians who have been unable to find factual support for these theories and those who have seen many instances in which an erroneous diagnosis of enlarged thymus was made in the case of a young person are entitled to hold the view that claims for the existence of these conditions are unfounded.

#### REPORT OF CASES

We shall report two interesting cases which show that not only may the diagnosis of enlarged thymus be erroneously made but that even when rather complete study and investigation have been carried out the true cause of dyspnea and stridor may be overlooked.

**CASE I.**—A boy aged eight weeks, was brought to the clinic on October 10, 1938. The family history was irrelevant. The patient had weighed 8 pounds (3.6 kg.) at birth and his delivery had been normal. He had nursed poorly and had had to be fed with a tube. He had been kept in the hospital for three weeks after birth. At the time of his dismissal, he had appeared to be in good physical condition.

Stridor developed when the child was five weeks of age. This increased in severity and dyspnea developed. The dyspnea became so severe that the accessory muscles of respiration were being used. When the child was brought to the Clinic, the stridor was chiefly inspiratory. The results of examination of the thorax were essentially negative. Laryngoscopic examination revealed some flabbiness of all of the supraglottic structures. The arytenoids were somewhat reddened. The child was placed in an oxygen tent but continued to have dyspnea and later cyanosis. Death took place three days after his admission. Although death from congenital relaxation of the larynx has not been encountered previously, it was thought that this was the cause of death in this case. However,

necropsy revealed a napkin ring like tumor in the subglottic region which on microscopic examination was found to be a hemangio-endothelioma.

CASE 2—A girl, aged nine weeks, was brought to the Clinic because of vomiting. The family history was irrelevant. For the first two weeks of life she had retained all feedings but had not gained any weight. She had had a peculiar wheezing respiration which had persisted. It occurred only intermittently when she was brought to the Clinic. Two weeks after birth she had begun to vomit. Emesis had become projectile. When she was seven weeks of age a Rammstedt operation had been performed. A thickened pylorus had been found. Emesis had continued after operation and there had been a progressive loss of weight. Roentgenograms of the thorax were essentially normal including the appearance of the heart and the region of the thymus gland. Roentgenographic examination showed a large stomach that was filled with gas. As cretinism was suspected,  $\frac{1}{8}$  grain (0.008 gm) of thyroïd was administered for a few days but did not produce any improvement.

The infant was greatly emaciated and weighed 2,870 gm. There were great irritability and hyperactivity. Respirations were grunting. Breath sounds were harsh in both lungs and bronchial in character over the apex of the right lung. There were numerous spots caused by thrush on the mucous membranes of the tongue and pharynx. There was evidence of some obstruction of respiration with inspiratory stridor. Laryngoscopic examination revealed an essentially normal larynx. The obstruction to respiration became more severe and an intratracheal tube was inserted. This produced an adequate airway but tracheotomy eventually became necessary. When the trachea was opened, some hard bloody crusts were coughed up and this enabled the baby to breathe easier. The surgical notes were as follows: "The obstruction is undoubtedly due to exudate in the trachea or bronchi." At the time the child was admitted to the hospital, a roentgenogram of the thorax showed some diminution in density of the right lung and partial atelectasis. The roentgenogram of the abdomen showed considerable gas throughout the intestinal tract. The pattern was not that of obstruction. A roentgenogram of the thorax made twenty days after her admission was normal. Temporary improvement followed supportive treatment, transfusions of blood and subcutaneous administration of fluids. Thirty days after her admission the temperature suddenly rose and death took place on the following day. Necropsy revealed a large cyst of the thyroglossal duct at the base of the tongue.

#### REFERENCES

- 1 Boyd, Edith. Growth of the thymus, its relationship to status thymicolymphaucus and thymic symptoms. *Am J Dis Child* 33 867-879 (June) 1927
- 2 Boyd, Edith. The weight of the thymus gland in health and in disease. *Am J Dis Child* 43 1162-1214 (May) 1932
- 3 Boyd, Edith. Weight of the thymus and its component parts and number of Hassall corpuscles in health and in disease. *Am J Dis Child* 51 313-335 (Feb) 1936
- 4 Hudson, H W, Jr. The thymus superstition. *New England J Med* 212 910-913 (May 16) 1935
- 5 Jackson, C L and Bowman, J E. Discussion. *Am J Dis Child* 54 1426-1427 (Dec) 1937
- 6 Kennedy, R. L J and New, G B. Chronic stridor in childhood, sometimes erroneously attributed to enlargement of the thymus. *J.A.M.A.* 96 1286-1289 (Apr 18) 1931
- 7 Morse, J L. The thymus obsession. *Boston M & S J* 197 1547-1552 (Feb 16) 1928

- 8 Pancoast, H K. Roentgenology of the upper respiratory tract, with special reference to enlarged thymus and its differential diagnosis Proc. Inter-State Postgrad M A North America, pp 206-216 1929
- 9 Pancoast, H K.. Roentgenology of the thymus in infancy and differential diagnoses of enlarged thymus and its treatment. Am. J M Sc. 180 745-767 (Dec.) 1930.
- 10 Wasson, W W.. The thymus gland Arch Otolaryng 4 495-511 (Dec.) 1916
11. Wilson T G The thymus myth Irish J M Sc. s. 6 (Mar ) 1938 pp 113-117

# NONSURGICAL EMERGENCIES OF THE RESPIRATORY TRACT IN CHILDHOOD

GEORGE B. LOGAN

**DIFFICULTY** in breathing on the part of a child is always an alarming symptom and one that almost always demands prompt measures for relief. It may be due to interference with either inspiration or expiration or both and the cause may be disease of some part or parts of the tubular air passages or of the lungs.

Difficult inspiration is generally caused by disease of the larynx or adjacent structures which may be based on inflammation or presence of a membrane, tumor or foreign body. Infants and young children whose trachea and bronchi are of small caliber exhibit evidence of serious obstruction more readily than do older children and adults. The classical signs of laryngeal obstruction are retraction above the suprasternal notch and clavicles and of the epigastrium. Inspiratory stridor and retraction of the intercostal spaces are also often present.

## CROUP

Spasmodic croup is one of the most common causes of inspiratory difficulty in young children. The onset is usually sudden and at night after the patient has been asleep for a time. However, symptoms may appear in the daytime. Croup may be preceded by an apparently mild infection of the respiratory tract. A harsh, brassy cough and inspiratory stridor are the initial symptoms. Some or all of the symptoms of laryngeal obstruction are usually present. The voice sounds become hoarse or disappear. There is rarely any associated fever. The symptoms, especially in young children, become progressively worse, but after several hours they generally subside spontaneously. They may, however, be relieved in a short time by the concomitant use of steam inhalations administered in a croup tent and antipyrine orally. Approximately 1 grain (0.065 gm) of antipyrine for each year of the child's age, to the age of five years, is a safe and effective dose. This may be repeated in an hour and at four hourly intervals thereafter, if necessary. The use of a teaspoonful of syrup of ipecac as an emetic is sometimes useful if the need for relief seems more urgent or if the steam inhalations fail to bring prompt relief. Bed rest in a room in which the atmosphere is warm and moist is advisable for a day or two after the initial attack since sometimes the difficulty recurs on one or more successive nights. Intubation or tracheotomy is practically never necessary.

## LARYNGOTRACHEOBRONCHITIS

If the symptoms of croup are not alleviated after a few hours of treatment, the probability that they may be caused by acute laryngotracheobronchitis should be seriously considered. If this condition is

present, the dyspnea will persist or become progressively more severe. Fever and evidence of marked toxicity often appear early, especially if the patient is a small infant. The borderline between croup and acute laryngotracheobronchitis is not easily drawn.

Laryngotracheobronchitis is best treated in a hospital since tracheotomy or bronchoscopy or both frequently are necessary. High moisture content of the inspired air, which is best secured by use of a steam tent or a steam room, is essential. Oxygen should be well moistened, if its use becomes necessary, since unmoistened oxygen exerts an undesirable drying effect on the secretions of the respiratory tract. A water vaporizer may be used as an adjunct to the oxygen tent, as described by Davison. If this apparatus is not available, the oxygen may be moistened by suspending wet cloths in the ice compartment of the oxygen tent.\* Steam may be run into the oxygen tent by pipe or rubber hose. This latter method, however, is cumbersome and not very satisfactory. The fluid intake should be kept at an adequate level. If the patient cannot take fluids by mouth, they should be given by the intravenous or subcutaneous route.

Sulfadiazine should be given in divided doses, about 1 to 2 grains (0.065 to 0.13 gm) per pound (0.5 kg) of body weight every twenty-four hours. The initial dose is best given by injecting it subcutaneously in the form of a 5 per cent solution of the sodium salt. Subcutaneous administration may be continued if the child refuses to take the drug by mouth. Regulation of the amount of sulfadiazine after the first twenty-four hours is determined by the patient's clinical course and the amount of the drug in the blood. If the child is able to take fluids by mouth, use of a saturated solution of sodium or potassium iodide is worth while as an additional means of keeping the secretions of the respiratory tract as fluid as possible. Five drops three times daily generally can be given to a child aged two years. The administration of atropine is contraindicated. The use of sedatives is generally inadvisable because such preparations may obscure the indications for tracheotomy. At the Clinic we prefer tracheotomy to intubation. The air entering the tracheotomy tube must be moist, this aids greatly in the prevention of crusts that tend to form in the trachea. The best apparatus for producing oxygenated vapor is a nebulizer which is attached to a tube that carries oxygen as described by Albers. In our experience, this measure has been lifesaving but this may not entirely obviate the need for bronchoscopic aspiration after

A small quantity of ice is left in the bottom of the ice compartment of a standard oxygen tent; this supply should be replenished frequently. A humidifier can be made by placing 8 to 10 inch legs under a shallow pan of water. A 10 inch handle is put over the top of the pan, over which can be suspended several lengths of gauze which dip into the water on the two sides. If gauze is unavailable, one or two wet bath towels, which must be moistened frequently are hung in the partially filled ice compartment. Boothby has estimated that this procedure will produce humidity of 70 to 80 per cent.

tracheotomy Bacteriologic examination of the tracheal secretions always should be made at the time of tracheotomy

#### DIPHTHERIA

Laryngeal diphtheria as a cause of inspiratory difficulty always should be considered If diphtheria of the nose or throat has been diagnosed, the laryngeal complication should be looked for In many instances the first sign of diphtheria is the insidious onset of croup which frequently occurs in the daytime The dyspnea is progressive and the nocturnal croupiness does not subside The voice sounds become hoarse and the child often becomes aphonic The previously described signs of laryngeal obstruction appear As the condition progresses, expiratory difficulty also may be noted In all cases in which diphtheria is suspected, swabbings of the throat should be cultured on appropriate media In many instances of laryngeal or tracheal diphtheria, cultures may fail to reveal *Corynebacterium diphtheriae* If the presence of diphtheric infection is suspected, diphtheria antitoxin should be administered without waiting for the results of the cultures

The same general plan of treatment as previously outlined for laryngotracheobronchitis may be used in the treatment of patients who have diphtheria of the larynx However, instead of the sulfonamides, diphtheria antitoxin should be administered as early as possible If the disease is mild or moderately severe from 20,000 to 40,000 units of antitoxin should be given If the patient is seriously ill from 40,000 to 80,000 units should be administered The intramuscular route is preferable but if the child is extremely ill the serum should be administered intravenously It is always wise to give what may appear to be an unnecessarily large dose rather than to give a dose that may be inadequate One large dose of antitoxin given early in the course of the disease should suffice, but it may be repeated in several hours if necessary Needless to say, sensitivity to the serum to be used should be determined by preliminary skin test or by the ophthalmic test If the results of these tests are positive, the usual precautions must be observed to prevent severe or serious reactions

The use of penicillin in the treatment of cases of diphtheria is still in the experimental stage but at present it does not appear to be effective

#### FOREIGN BODY, PAPILLOMA

A foreign body or an incarcerated pedunculated papilloma may be present in the larynx and produce signs of respiratory obstruction Diagnosis of such a condition may require direct laryngoscopic examination or possibly bronchoscopic examination Roentgenographic examination of the upper part of the respiratory tract may be helpful

#### ASTHMA

The most important cause of expiratory difficulty is asthma A feeling of tightness in the chest, dyspnea, wheezing and cough are its

most common symptoms. Auscultatory examination of the chest reveals sibilant and sonorous râles which are most notable during the expiratory phase. The expiratory phase of respiration is prolonged and the normal pause between inspiration and expiration is generally absent. Except during the initial attack, the diagnosis is frequently made by the parents.

The best drug for the immediate relief of an asthmatic attack is epinephrine (adrenalin chloride). An aqueous solution of 1:1,000 is administered subcutaneously. It is rarely necessary to give a child a dose greater than 0.5 c.c. Several small doses at intervals are more effective and better tolerated than a single large dose. The drug also may be administered in peanut oil or in a gelatin mixture, the dose being the same as of the aqueous solution. The theoretical advantages of the peanut oil or gelatin preparation are slowness of absorption and relatively prolonged action. The oil preparation however often fails to exhibit these advantages and furthermore the oil itself occasionally causes allergic reactions.

Epinephrine also may be administered in a 1:100 solution by means of a nebulizer. A few drops of the solution are placed in the all-glass or plastic nebulizer, which is a special type of atomizer, the nozzle is directed down the patient's throat, and the bulb is squeezed as the patient inspires. One or two squeezes during each of three to five inspirations will generally suffice. For small children the nebulizer can be operated by an adult; older children learn easily to use it themselves. Untoward reactions to epinephrine are rarely seen even when the drug is used repeatedly in this manner.

Ephedrine hydrochloride or sulfate, which is given in capsule form by mouth, is often effective in controlling asthmatic attacks. It may be given to small children as a powder in syrup or jelly. The dose for older children is  $\frac{3}{8}$  grain (0.024 gm.) for younger children,  $\frac{3}{16}$  grain (0.012 gm.) or less may be effective. One-half to  $\frac{3}{4}$  grain (0.032 to 0.05 gm.) of one of the barbiturates is administered concomitantly to combat the stimulating effect of the ephedrine as well as to calm the patient.

Propadrine hydrochloride (di-phenyl-1-amino-2-propanol-1-hydrochloride)  $\frac{1}{10}$  to  $\frac{1}{4}$  grain (0.012 to 0.050 gm.) orally every three or four hours may be tried. This drug is considered by some authors to produce fewer untoward reactions than does ephedrine.

Aminophylline may be used orally, rectally or intravenously. It is of value for patients who do not react favorably to epinephrine. Some authors consider aminophylline more useful in the prolonged attack than in the acute attack. I have found that it may be of value in both conditions. Several commercial preparations of the drug are designed for oral use are available in either the pure form with a barbiturate or with a barbiturate and ephedrine.

Suppositories of aminophylline combined with one



rates in a cocoa butter base are frequently useful. The action of the drug when it is so administered is slower but somewhat more prolonged than when given orally or intravenously. Aminophylline,  $3\frac{3}{4}$  grains (0.25 gm), together with seconal sodium (sodium propylmethylcarbonylallylbarbiturate),  $\frac{3}{4}$  grain (0.05 gm), may be given in this manner to children, aged two to ten years. Older children may require 5 to 7 grains (0.3 to 0.45 gm) of aminophylline. The drug also may be given in solution by rectal instillation. This mode of administration produces rectal irritation in some cases.

The intravenous administration of aminophylline produces a prompter effect than oral or rectal administration, however, it is important that it be given slowly. The dose for a ten year old child is  $3\frac{3}{4}$  grains (0.25 gm), about half this dose is given to small children. Aminophylline when given intravenously often is combined with glucose. Patients who have severe asthmatic attacks benefit from the intravenous administration of 100 to 300 c.c. of a 25 per cent solution of glucose. Larger amounts of a 10 per cent solution also are often effective.

Theophylline is combined with one of the barbiturates in one commercial preparation for oral use. In our experience at the Clinic, this preparation at times has proved beneficial.

The use of sodium or potassium iodide is of value especially in the treatment of prolonged attacks of asthma and as an aid in prevention. At the Clinic we use the saturated aqueous solution since variation of the dose can be made with ease and accuracy. The dose is varied according to age and degree of asthmatic difficulty, 5 drops three times daily being given to a child, aged four years. Older children who have severe asthma may be given 25 to 30 drops three times daily.

Oxygen administered in a tent or by mask is sometimes helpful. The combination of 80 per cent oxygen and 20 per cent helium is frequently very effective. Since this mixture is best given by mask, its use unfortunately is limited to those children who will tolerate a mask and for whom a small size mask can be secured. The administration of such an oxygen-helium mixture in a tent is not completely successful unless the tent is practically airtight.

In the treatment of patients who have status asthmaticus, the rectal administration of ether in oil is a useful procedure. Three to 4 ounces of ether mixed with an equal amount of warmed olive oil is instilled through a small rubber catheter. An amount smaller than the initial dose may have to be repeated at intervals of a few hours for twenty-four hours.

#### PNEUMONIA

Pneumonic processes may produce dyspnea which is not attributable to obstruction. The cause seems to be a combination of pain, toxicity and reduced vital capacity. Space does not permit detailed discussion of the different types of pneumonia.

The onset of primary or lobar pneumonia is characterized by fever, dyspnea and cough. The child's face is flushed, the ala nasi dilate with each inspiration and the respiratory rate is increased. This chain of events generally follows mild infection of the upper part of the respiratory tract. Children between the ages of about two and fourteen years who suffer from this type of pneumonia generally make a satisfactory recovery. The use of the sulfonamide compounds has lowered the already low mortality figures and also has decreased the morbidity. Their use in adequate dosage, that is, 1 grain (0.065 gm) per pound (0.5 kg) of body weight in twenty-four hours, therefore, is worth while. One-third to one-half of the drug is given as an initial dose and one-fourth of the twenty-four-hour dose is then given every six hours. The sulfonamide compound may be administered in a 0.5 or 5 per cent solution subcutaneously if necessary. Its use is continued for forty-eight hours after the temperature is normal and then often in half the usual amount for one or two days. Sulfadiazine is the current choice of these preparations.

The patient's fluid intake should be sufficient so that the urinary excretion remains adequate. The minimal intake of an infant should be 1,000 c.c. of fluid and that of a twelve to fourteen year old child should be 2,000 c.c. The diet should be as nearly normal as the patient will take. A daily bowel movement is desirable, chiefly because abdominal distention often develops in association with pneumonia. A daily enema may be necessary in the early part of the disease. A mild laxative such as milk of magnesia is often useful. When dyspnea is marked or when cyanosis occurs the administration of oxygen is indicated.

#### BRONCHOPNEUMONIA

Bronchopneumonia is the most serious type of pneumonia of infants and young children. It may complicate communicable diseases such as measles, or it may be secondary to infection of the respiratory tract. Fever and cough are often the chief symptoms. Dyspnea may be absent or marked, it is generally marked in infants. The disease may be acute and overwhelming, especially in poorly nourished infants or in those who are convalescing from other diseases.

The treatment is essentially the same as that outlined for primary pneumonia. The use of oxygen is often necessary early in the course of the disease. Transfusions of small amounts of blood are sometimes helpful, especially in the case of a debilitated infant, if the procedure can be carried out without excessive pain or discomfort.

One form of bronchopneumonia has been termed "capillary bronchitis" by many authors because of the predominant involvement of the terminal bronchioles. Auscultation reveals many fine rales in part or all of the lungs. Dyspnea is severe and sometimes cyanosis occurs. Although many clinicians have abandoned the use of the mustard pack at the Clinic we continue to find it effective in this type of case.

A double handful of mustard is placed in a dishpan of water. This mixture is stirred and heated slowly until the fumes become irritating to the eyes. Then the pan containing the mixture is removed from the stove. A small blanket is soaked in the solution and then wrung partly dry. The patient is wrapped in this, care being taken to see that the blanket is wrapped completely around the arms and legs as well as around the body, covering the body from the neck down to and including the feet. The patient is covered with a dry blanket and allowed to remain in this pack for one-half to three-fourths of an hour or until the skin becomes pink. The patient then is removed from the moist blanket and wrapped in a warm blanket with a hot water bottle placed at the feet and allowed to remain in this warm dry pack for another hour. While the pack is being applied, the patient should be given cool water or other cool drink.

The remainder of the treatment is the same as for other types of pneumonia. The recommendations previously made for prevention of drying of secretions in the respiratory tract in the presence of laryngotracheobronchitis are often applicable to this type of case.

#### REFERENCES

- 1 Albers, G. D. Use of a nebulizer to produce oxygenated vapor: report of case of acute laryngotracheobronchitis. *Proc. Staff Meet., Mayo Clin.* 18:511-514 (Dec. 29) 1943.
- 2 Boothby, W. M. Personal communication to the author.
- 3 Davison, F. W. Treatment of acute laryngotracheobronchitis. *Arch. Otolaryng.* 32:321-330 (Aug.) 1940.

# CARDIAC EMERGENCIES IN PEDIATRIC PRACTICE

HADDOW M KEITH

THERE are relatively few times when heart disease is severe and acute enough to be called an emergency. The following five conditions may be included in this category (1) direct trauma, (2) asthma accompanied by heart disease (3) pericardial effusion, (4) acute cardiac failure and (5) paroxysmal tachycardia.

## DIRECT TRAUMA

Direct trauma is rare and is due to bullet wound or penetration by a sharp object. Treatment is essentially surgical with suturing of the heart muscle if possible and supportive treatment with transfusions of blood and infusions of solution of glucose or of glucose and sodium chloride.

## ASTHMA ACCOMPANIED BY HEART DISEASE

In the presence of acute or chronic cardiac disease, the occurrence of an asthmatic attack may precipitate an emergency. Rapid relief of the asthmatic attack may be obtained by means of epinephrine administered subcutaneously. Cyanosis and in particular, dyspnea may be relieved by placing the patient in a helium-oxygen or oxygen tent. The effect of epinephrine may be prolonged by the use of ephedrine. Absolute rest in bed is, of course, essential and morphine may be of great help in keeping the patient as quiet and comfortable as possible. Aminophylline may also be used intravenously,  $3\frac{3}{4}$  grains (0.25 gm) being given to a child of six to ten years (See emergency treatment of asthma).

## PERICARDIAL EFFUSION

Pericardial effusion is fairly common among children and may at times constitute an emergency. It is usually due to an acute infection of the pericardium with much sepsis and toxicity. In addition much of the distress is due to the so-called tamponade of a large collection of fluid including hemopericardium. Willis<sup>2</sup> stated that in approximately 68 per cent of all cases pericardial effusion is due to the acute infectious type of disease and that it occurs secondarily to other intrathoracic infections: pneumonia, empyema, mediastinitis, acute non-tuberculous pleuritis and pulmonary abscesses. In rare cases it may be secondary to a puncture wound, rupture of a subdiaphragmatic abscess into the pericardium and so forth. It may also be the result of foci of infection in other parts of the body and may follow scarlet fever, typhoid fever and so forth.

The diagnosis of acute pericarditis when the patient is a child is not always simple and it is particularly difficult when the patient is an

infant A friction rub may be audible but with the rapid collection of fluid this may not be present When children have pneumonia or other acute infection, acute pericarditis may be kept in mind as a complication In such cases sudden embarrassment of the circulation with some muffling of the heart sounds and increase in the cardiac dullness, both to right and to left, is suggestive The apical impulse may become feeble and diffuse but the pulse may remain strong in spite of the diminished intensity of the cardiac sounds Dullness with evident bronchial breathing may be present at the angle of the left scapula Roentgenoscopic examination may be helpful, revealing the large globular or "onion" shaped heart with absence of pulsations of the margins Fever and leukocytosis may persist with improvement in, or disappearance of, the primary infection Further evidence in favor of a large effusion is increase of venous pressure, with, possibly, enlargement of the liver

In addition to acute purulent pericarditis the tamponade effect may occasionally be produced suddenly in acute fibrinous pericarditis and even less frequently in tuberculous pericarditis The symptoms and signs are much the same as in purulent pericarditis, with the exception that evidence of other acute infection may be lacking in the fibrinous form and will be lacking in the tuberculous type

**Treatment**—When this condition becomes an emergency, immediate treatment by paracentesis of the pericardium or, in certain cases, cardiolysis will relieve the patient at once These are surgical procedures, the technic of which will not be described here Morphine may be used in sufficient amount to insure adequate rest When there is definite purulent infection, sulfadiazine may be given intravenously or by mouth in sufficient amount to maintain the blood level between 15 and 25 mg per 100 c c of blood or penicillin may be used

Rheumatic pericardial effusions usually subside spontaneously and rarely require paracentesis

In cases of tuberculous pericarditis, temporary relief from the tamponade effect may also be given by paracentesis

#### ACUTE CARDIAC FAILURE

Acute myocarditis with failure may be present as an emergency Such a patient is restless and in great distress, with dyspnea, cyanosis, enlargement of the heart and all the evidences of congestive failure, for example enlarged liver, moisture in the lungs, pleural effusion, ascites or edema He will prefer to be propped up in an almost vertical position or leaning forward on a firm support

My colleagues and I recently had occasion to treat such a patient (a boy of seven years) He was kept in an oxygen tent for forty-eight hours and was given three ampules (2 c c each) of digifolin intravenously in the first twenty-four hours One-sixth grain (0.01 gm) of morphine sulfate was given at once and followed by  $\frac{1}{12}$  grain

(0.0054 gm.) when necessary. A transfusion of 125 c c of whole blood was given slowly, followed by a slow intravenous drip of 1,000 c c of 10 per cent solution of glucose.

On the third day the oral administration of  $1\frac{1}{2}$  grains (0.1 gm.) of digifortis was begun and was continued daily until the twenty-first day. After this all medication was discontinued and the patient made an apparently complete recovery.

#### PAROXYSMAL AURICULAR TACHYCARDIA

Paroxysmal auricular tachycardia is rare in children but may be successfully treated. In 1942 a twenty months old baby was admitted to the hospital because of a very rapid heart rate. No etiologic factor could be determined. Three weeks previously he had had a similar attack. The electrocardiogram showed evidence of auricular flutter, the heart rate being 258 beats per minute. The patient was given intravenously 1 c c of cedilanid (lanatosid-C) containing 0.2 mg. or 0.8 cat unit per cubic centimeter and this was repeated in one hour. Three hours later the heart rate was approximately 130 beats per minute and the patient appeared well. This is in agreement with the experience of Hubbard.<sup>1</sup>

#### REFERENCES

1. Hubbard, J. P. Paroxysmal tachycardia and its treatment in young infants. *Am. J. Dis. Child* 61:687-709 (Apr) 1941.
2. Willis, F. A. Some cardiac emergencies. *M. Clin. North America* 22:895-906 (July) 1938.

# MANAGEMENT OF NONSURGICAL EMERGENCIES ASSOCIATED WITH THE URINARY TRACT OF CHILDREN

ROGER L J KENNEDY

MANY emergencies due to conditions in the urinary tract of children are essentially urologic or surgical problems. The physician, however, must possess a knowledge of the procedures necessary for their recognition and treatment.

A sudden sharp reduction in the amount of urine excreted by an infant or child calls for immediate consideration of its cause. Conditions, such as obstruction of the posterior urethra and vesical neck or obstruction due to calculi or neoplasms can usually be ruled out by the history, physical examination and catheterization or, if it is necessary, by cystoscopic examination. Likewise, inability to urinate may be due to neurologic disturbances, such as traumatic, inflammatory or neoplastic myelitis, but the cause in such cases should be evident. The finding of an overdistended bladder furnishes evidence that the anuria or oliguria is probably not dependent on inability of the kidneys to secrete urine. The conditions just mentioned cannot be considered strictly medical emergencies and, therefore, will not be considered here.

Occasionally a medical problem involving other systems or organs of the body may account for marked decrease in the output of urine. Cardiac decompensation which is discussed elsewhere in this volume is an example of such a condition.

In the infant or young child particularly, dehydration resulting from diarrhea or vomiting may require special treatment to overcome the gastro-intestinal disturbance and incidentally to restore sufficient fluid to the patient in order to re-establish renal excretion. Occasionally anuria or oliguria may be due to thrombosis of the renal veins. Although there is no effective treatment for this condition its presence may be suspected if abdominal pain and hematuria have been followed by cessation of the secretion of urine and frequently by the passage of clots of blood.

Transfusion reactions too occasionally are the cause of suppressed renal function.

## NEPHRITIS, NEPHROSIS AND CERTAIN OTHER CONDITIONS

After exclusion of the conditions considered thus far the chief problem in the management of medical emergencies associated with the urinary tract of children is the determination of the type of renal disease that is accountable for the decreased output of urine. If oliguria manifests itself during or shortly after an acute infectious disease, such as tonsillitis, scarlet fever or pneumonia, the probability that acute

nephritis is present, becomes great. If other symptoms, such as edema of the face and ankles, slight or moderate elevation of blood pressure and, if sufficient urine is obtainable for examination, albuminuria and hematuria, are found, the diagnosis becomes practically certain. Although more complicated chemical analyses, such as the determination of the value for blood urea, may tend to confirm the diagnosis, they usually are not necessary.

Faced with such a situation, the physician will do well to explain to the parents that the outlook in such cases is generally good and that the condition tends to correct itself even in the absence of any therapeutic measures. While it has been customary to reduce the amount of protein in the diet to about a gram of protein per kilogram of body weight per twenty-four hours and to decrease the allowance of salt and liquids it is questionable whether such measures are imperative or even necessary. The question as to the degree to which liquids need be restricted has received a good deal of attention in the past. It is now generally agreed that the amount of liquid permitted may be governed by the desire of the individual patient. If the oliguria persists or anuria develops, an attempt to establish diuresis may be made by the intravenous injection of 100 to 300 c.c. of an 8 per cent solution of sucrose. The use of mercurial diuretics in such cases usually is contraindicated.

The necessity for inducing diuresis may become especially urgent if convulsions (thought to be due to edema of the brain) occur. An attempt then may be made to induce diuresis either by the use of sucrose as just mentioned or by the intramuscular injection of magnesium sulfate. The dose of magnesium sulfate may be 0.2 gm. per kilogram of body weight in a 10 or 25 per cent solution. The injection may be repeated once or twice.

Occasionally, particularly at its outset, acute diffuse pyelonephritis may be accompanied by suppression of the renal function sufficient to cause anuria or marked oliguria. It is important to overcome this condition as promptly as possible. The intravenous administration of an 8 per cent solution of sucrose in half strength Ringer's solution may bring about desired diuresis.

Oliguria or anuria may develop during the course of so-called nephrosis which in its typical form is characterized by edema, anasarca, albuminuria, the appearance of doubly refractive bodies in the urine and by elevation of the serum lipids. In my experience this disease in its pure form is seldom encountered in children except at the onset. Some time during the disease erythrocytes appear in the urine and retention of nonprotein nitrogen in the blood takes place. These findings indicate that nephritis is present. With the development of oliguria and anuria the edema and the ascites increase concomitantly and sometimes hydrothorax develops. The prevention of anuria or oliguria and the concomitant prevention of increasing retention of water are thought to be favored by a diet which contains 2.5 to 3 gm. of protein



per kilogram of estimated body weight for twenty-four hours and the elimination of nearly all the salt (not more than 2 gm of salt daily)

If anuria or oliguria develops in spite of these measures, one or more of the following measures may be employed. Thyroid extract may be administered. In the beginning the dose is 1 grain (0.065 gm) daily, this is increased at intervals of three to four days by 1 grain (0.065 gm) until 6 (0.4 gm) or more grains are given each day or until diuresis or diarrhea occur. Potassium nitrate may be given in doses of 10 to 15 grains (0.65 to 1 gm) three times daily to a child three years of age. This amount may be increased to 15 or 30 grains (1 to 2 gm) three times a day. Ammonium chloride also may be tried. The initial dose may be 5 grains (0.3 gm) three times a day and this may be increased gradually until the pH of the urine is 5.0 (tested with nitrazine paper). The administration of urea by mouth also may be employed. The dose is 20 to 100 gm daily. The diuretics, such as theobromine, theophylline, theocalcin, theocin and aminophylline, occasionally seem to be effective. If the mercurial diuretics, such as salyrgan or mercurpurin, are used, the initial dose should be small. The initial dose of salyrgan may be 0.25 cc given intramuscularly. After this dose has been given, signs of renal irritation (hematuria) should be looked for. If none are evident after two or three days, 0.5 cc may be given. With this care the dose may be increased gradually to 2 cc. If diuresis does not occur after the injection of 2 cc, use of the drug should be discontinued. A similar plan should be used if mercurpurin is employed. Intravenous transfusions and infusions have been employed with variable results. Fairly large transfusions of whole blood (20 to 30 cc per kilogram of body weight or 10 to 15 cc per pound of body weight) may be given and should be repeated at relatively frequent intervals. Plasma may be used in place of whole blood. Lyophil serum in a concentration of 4:1 has been used successfully but I have observed some undesirable reactions following its use.

A not uncommon development during nephrosis is peritonitis or the so-called peritoneal syndrome characterized by fever, abdominal pain and tenderness. The use of sulfonamides, preferably sulfadiazine, is indicated and effective in the control of this condition. If the blood urea is elevated, care must be observed to avoid undesirably high concentrations of the drug in the blood. Since the infecting organism is most commonly pneumococci (less frequently streptococci), penicillin may be tried in place of the sulfonamides. To date I have had no experience with penicillin in treating this syndrome.

Another condition that may develop in nephrosis is the so-called erysipeloid lesion which, as the name implies, is a condition of the skin similar to, and possibly identical with, erysipelas. Sulfonamides, penicillin and in some cases, anti-scarlatinae streptococcic serum may be used in treatment.

## COMPLICATION OF TREATMENT WITH SULFONAMIDES

From an early period in the use of the sulfonamides it has been recognized that their use may be followed by the accumulation of large numbers of crystals in the kidneys with consequent obstruction in the ureter, renal pelvis or tubules. Not infrequently this reaction is accompanied by renal colic. Prompt discontinuance of doses of the drug and oral and intravenous administration of large amounts of fluid usually re-establish the flow of urine but sometimes irrigation of the renal pelvis and ureters is necessary. The occurrence of this condition does not necessitate the permanent discontinuance of the use of sulfonamides but requires that they be given in smaller amounts with careful observation to make sure that sufficient urine is excreted and that the level of the drug in the blood does not become excessive. The concomitant administration of alkali in the form of sodium bicarbonate is thought by some physicians to decrease the possibility of the development of this undesirable condition.

## CERTAIN MECHANICAL OBSTRUCTIONS IN THE URINARY TRACT

Mechanical obstructions may occur in the urinary tract which do not call for the services of the urologist or surgeon. Ulceration at the external urethral meatus and of the surrounding glans penis in the male may cause acute retention of urine. The use of compresses moistened in warm solution of boric acid will usually soften the crust which may be removed and allow the urine to be expelled. A similar condition may develop when a redundant prepuce becomes inflamed. Either the resultant discomfort occasioned by urination or occlusion by inflammatory reaction may account for the retention. Again the application of warm wet boric acid compresses may be sufficient to relieve the condition, at least temporarily. Subsequent circumcision is usually indicated.

Paraphimosis due to constriction of the retracted prepuce and consequent edema may be sufficiently marked to interfere with urination. The accepted procedure in such cases is the application of an ice cap or cracked ice wrapped in several layers of cotton material. After a few hours of such application the edema usually has subsided enough so that the prepuce may be drawn forward over the glans. Then the residual edema can disappear. Occasionally a dorsal slit through the redundant portion of the prepuce and the constricting band may be necessary for relief. An incident of this sort is usually considered an indication for subsequent circumcision.

# ACUTE NONSURGICAL EMERGENCIES RELATED TO THE GASTRO-INTESTINAL TRACT

GEORGE B LOGAN

ABDOMINAL pain, vomiting, diarrhea and evidence of gastro-intestinal bleeding are symptoms for which urgent medical attention is often sought. These symptoms may occur singly or in varying combinations. Certain of the disease conditions which cause these symptoms in infancy and childhood will be discussed.

Some of these symptoms are the result of conditions which are treated surgically. However, the diagnosis of the condition and the decision as to the need of surgical care must be made by the physician who first sees the patient.

The ingestion of poisons will be dealt with only briefly in this paper.

## COLIC

Colic, strictly speaking, refers to any acute abdominal pain. In pediatric practice the unqualified term generally is used to denote the presumed recurrent abdominal pain observed in many infants. The word "presumed" is used advisedly since when an infant has recurring spells of crying in which he flexes his thighs on his abdomen this act is interpreted as indicating the presence of acute abdominal pain. This interpretation undoubtedly is often correct. However, there is some evidence that hard crying in early infancy is a reaction to other stimuli. My associate, Dr C A Aldrich, has said that it is more properly termed "compulsion crying." As the infant matures the compulsion crying stops. This is to be expected at the age of about three months. The so-called three month colic may be explained in this way.

Further discussion of the etiology and pathogenesis of colic would be in the realm of individual speculation and experience. The incomplete raising of air swallowed during the course of feeding, intolerance to certain foods and fatigue have all been individually or collectively found to be important.

There seems to be a higher incidence of colic among the infants of constitutionally nervous or high strung parents than among those of a more phlegmatic nature.

The crying spells may occur at a regular time of the day such as early evening or 2 to 3 a m, or they may occur at intervals throughout the twenty-four hour period. The grandmother or mother usually makes the diagnosis and the physician is summoned only when the use of various home remedies has failed. It is the physician's first duty to ascertain that no organic cause for the colic, such as intussusception or incarcerated hernia, is present. Gentle rubbing of the abdomen, the application of heat and an enema generally will relieve

the immediate situation. The use of phenobarbital,  $\frac{1}{8}$  to  $\frac{1}{4}$  grain (0.008 to 0.016 gm.), or a few drops of camphorated tincture of opium may be necessary. Atropine sulfate, 1 to 3 minims of a 1:1,000 aqueous solution, often is helpful. Various carminatives such as soda mint, cinnamon water and peppermint water have been used.

As a means of preventing further attacks the various etiologic factors previously mentioned should be investigated. Some infants do not tolerate orange juice. A daily dose of 25 mg. of ascorbic acid is an effective substitute. A change of formula, if the infant is not breast fed, might be tried. Suggested changes are trial of another carbohydrate, evaporated milk, acidified milk or protein milk. It is unwise, however, to make frequent changes of formula. In the rare instance of persistent and uncontrolled crying it is necessary to hospitalize the infant so that the mother and other members of the family can get some rest.

#### APPENDICITIS

The diagnosis of acute appendicitis is often difficult. The so-called classic symptoms of the disease, that is, generalized abdominal or epigastric pain migrating to the right lower quadrant of the abdomen, nausea and often vomiting and slight elevation of temperature, frequently do not all occur together.

In the case of a child, abdominal pain, especially if located in the right lower quadrant, should always suggest appendicitis regardless of whether it is associated with nausea, vomiting, diarrhea or fever. The most reliable sign is local tenderness over McBurney's point. Muscle spasm, rebound tenderness and tenderness on the right when a rectal examination is performed may or may not be present. The indiscriminate removal of the appendix of every child who has abdominal pain is not advisable but if tenderness in the right lower quadrant of the abdomen can be demonstrated the wisest procedure is appendectomy.

The leukocytes often are increased in patients who have acute appendicitis and there is an actual increase of the neutrophilic polymorphonuclear cells. However the leukocyte count may not be elevated. This blood examination should be used as a minor rather than as a major diagnostic aid in helping to confirm the clinical diagnosis.

A child who has pneumonia may have abdominal pain as an initial complaint. There may be no physical or roentgenologic signs of the pneumonic process. Fever is usually present. The leukocyte count often is elevated to 20,000 or 40,000 cells per cubic millimeter of blood, which is unusually high for the onset of acute appendicitis. The superficial abdominal tenderness noted in pneumonia is not increased by deep palpation. Rectal tenderness is not elicited in the presence of pneumonia. In a few instances it has been impossible to distinguish between appendicitis and the abdominal pain associated with pneumonia. Occasionally the two conditions coexist. When real

doubt exists as to which disease is present it is better to remove a normal appendix from a child who has pneumonia than to allow an appendix to rupture in a child presumed to have pneumonia

### INTUSSUSCEPTION

Intussusception is a condition for which surgical treatment is urgent. Therefore, an early, accurate diagnosis should be made. Children of any age may have this condition but it is more common in those less than two years of age. The most characteristic symptom of intussusception is recurrent cramping abdominal pain. The pain generally occurs regularly at intervals of a few minutes. Sometimes the recurrent pain is noted for one or more hours and then ceases for several hours. Infants manifest the pains by crying spells. An abdominal mass and rectal bleeding eventually are noted. It is better to make the diagnosis before this occurs.

Many instances have been reported in which intussusception inadvertently or intentionally was reduced by a barium enema given under the fluoroscope. If good surgical help is available, such a procedure is inadvisable. The pressure of the enema may not be well controlled and the condition of the bowel wall cannot be seen. If the enema fails to reduce the intussusception, operation has been that much longer delayed.

### ANAPHYLACTOID OR HENOCHE'S PURPURA

The onset of this condition is generally acute. The abdominal tenderness and pain may be either generalized or localized. Evidence of intestinal obstruction generally does not occur. Either vomiting or diarrhea or both may be present. One is aided in making the diagnosis if purpuric skin manifestations occur or if there is blood in the stool or vomitus. In some instances, purpuric lesions may be seen in the mucosa of the rectum and sigmoid at the time of proctoscopy. The abdominal pain, however, may be present for as long as seven days before any purpuric manifestations appear. In this type of purpura, the blood platelets are present in normal number and the bleeding and coagulation factors of the blood are normal. The Rumpel-Leede test is often positive. Sensitivity to food or other substances is considered by some authors as an etiologic factor.

Treatment is not satisfactory. There may be one or more recurrences of the disease. The initial attack may last several weeks with exacerbations and remissions. Acute nephritis or cerebral hemorrhage may occur as a complication. Edema involving the face and scalp, extremities and genitalia may be noted for short periods.

Blood transfusions may help. The use of moccasin snake venom has been recommended but its use may be attended by some unpleasant reactions. The abdominal pain may be controlled by the use of a hot water bottle but codeine,  $\frac{1}{2}$  to 1 grain (0.032 to 0.065 gm), morphine

sulfate,  $\frac{1}{16}$  to  $\frac{1}{8}$  grain (0.004 to 0.008 gm) or demerol (1-methyl 4-phenyl piperidine 4-carboxylic acid ethyl ester hydrochloride) 50 to 100 mg, often are necessary. Small doses (0.25 cc) of epinephrine chloride in 1:1,000 aqueous solution given subcutaneously at frequent intervals sometimes have been beneficial. The use of the same drug in oil or gelatin also may be tried. The administration of ascorbic acid (100 to 300 mg daily) vitamin P (citrin) and vitamin K (5 to 40 mg daily) have been suggested, as well as calcium lactate and salicylates. In severe cases there may be considerable weight loss. The use of parenteral fluids may be necessary. Small frequent feedings often are tolerated better than the customary three meals a day. Skin tests for sensitivity to various foods frequently are not of diagnostic assistance whether done by the scratch, intradermal or passive transfer method. If food sensitivity is considered an etiologic factor the offending food or foods have to be determined by history, observation or the use of an elimination diet. Recovery has been observed in cases in which no change of diet was made.

#### LEAD POISONING

Lead poisoning sometimes is encountered in pediatric practice. The more common sources of lead are dried paint or putty chewed from walls, window sills or cribs, ingestion of water carried by old pipes, use of storage battery casings as fuel in inadequately ventilated dwellings and contact with lead incident to the casting of lead soldiers or toys. Lead nipple shields are a source of lead to nursing infants. Cerebral symptoms are the most common manifestations of lead poisoning in children though intestinal colic has been observed. A zone of increased density generally can be demonstrated roentgenographically in the epiphyseal end of the diaphysis of the long bones. The knee and wrist are the best regions in which to demonstrate these changes. Basophilic stippling of the erythrocytes is often present. The most specific test is the spectroscopic demonstration of abnormal quantities of lead in the blood or the presence of over 100 micromilligrams of lead per liter in a twenty-four hour specimen of urine.

The pain of the colic may necessitate the use of morphine sulfate hypodermically. The proper dose for an adult is  $\frac{1}{8}$  or  $\frac{1}{4}$  grain (0.01 or 0.016 gm). The dose for a child may be computed by the formula

weight      age  
of  $\frac{\text{weight}}{150}$  or  $\frac{\text{age}}{\text{age} + 12}$ . The adult dose previously mentioned is multiplied by the fraction so secured.

Atropine sulfate hypodermically in doses of  $\frac{1}{160}$  grain (0.00043 gm) for a fourteen year old child and  $\frac{1}{400}$  grain (0.00022 gm) for an eighteen month old infant is often sufficient. Tincture of belladonna administered orally may be useful giving 2 minims to a year old infant and 20 drops to a fourteen year old child.

Inhalations of amyl nitrite may give transient relief from the pain.

## ACUTE DIARRHEAS

The diarrheal diseases of infancy and childhood are still encountered though not nearly as frequently as they were twenty-five years ago. Some of these are specific infections due to one of the dysentery or Salmonella organisms. In our practice diarrhea due to nonspecific or parenteral infections is much more frequently encountered. These diseases often are not sufficiently acute to require emergency treatment. However, in two situations prompt medical attention is necessary. The first condition generally is limited to children less than two years of age. This is the washed-out apathetic appearance which occurs suddenly after one or more days of diarrhea and vomiting. It may also appear after the passage of only one or two copious liquid stools. Infants so afflicted should be hospitalized promptly for the administration of intravenous fluids and transfusions. The second situation in which prompt medical attention is indicated is that in which abdominal pain is the initial or the most prominent complaint. This may occur at any age. Careful abdominal palpation will help to decide whether a surgical procedure is indicated. Acute appendicitis has been observed to follow an acute diarrheal episode.

Treatment of the diarrheal diseases may be grouped briefly into three parts: (1) diet regulation, (2) fluid administration and (3) medications.

Restriction of the diet depends on the severity of the disease. In the most severe cases, nothing is given orally for the first twenty-four hours. The time and amount of additions, starting with water, depend on the patient's age and condition. In the less severe infections an initial diet of grated or well-scraped apple and water or apple and boiled skim milk are sufficient restriction. Vitamin supplements given parenterally are often helpful.

The amount of fluid administered depends on the patient's age and the severity of the disease. In the more severe cases parenteral administration is necessary for many days. Continuous intravenous infusion is the most satisfactory method. In small infants scalp veins or small veins of the hand or foot are frequently the best to use. Surgical exposure of the ankle veins is seldom necessary. Infusions of bone marrow using the upper tibia in small infants or the sternum in older children have been extremely useful. Subcutaneous infusion is a useful adjuvant method of administering fluid. The intraperitoneal injection of fluid may be resorted to as an emergency procedure. The following solutions are suggested as being most valuable and readily available commercially if they cannot be prepared locally: isotonic saline (0.9 per cent), 5 per cent glucose in distilled water, 5 per cent glucose in isotonic saline,  $\frac{1}{6}$  molar sodium lactate solution and 10 per cent glucose in distilled water.

Ringer's solution and Ringer-lactate solution are valuable but are not always readily available. Sodium bicarbonate in 5 per cent solu-

tion may be employed as an alkalizing agent but it is more difficult to prepare, less stable and more prone to induce alkalosis than is  $\frac{1}{6}$  molar sodium lactate solution. The bicarbonate, however, is more prompt in action and is preferable in cases of circulatory failure, hepatic damage and extreme anoxia because the lactate may be oxidized too slowly. Sodium bicarbonate solution is to be given only when the carbon dioxide content of the blood is low and when this estimation may be repeated at regular intervals.

Two to 3 ounces (60 to 90 c.c.) of fluid per pound (0.5 kg.) of body weight is the usual daily requirement of an infant. This must be considered when planning the amount of fluid to be administered to a dehydrated baby. One ounce (30 c.c.) per pound (0.5 kg.) is a minimal amount of fluid to be administered daily to establish hydration in a clinically dehydrated child. As previously suggested, the continuous intravenous route is preferable especially when the patient is moderately or severely dehydrated. If facilities for frequent parenteral administration of fluid exist, "sets" of fluids may be given. These consist of an intravenous infusion and a hypodermoclysis. This method is of particular value when the urinary excretion is low. The hypodermoclysis of isotonic saline,  $\frac{1}{6}$  molar sodium lactate solution or Ringer-lactate solution, is started first. Then 10 per cent glucose in distilled water is given intravenously. In the case of an infant who weighs up to 12 to 14 pounds (5.4 to 6.4 kg.), 20 c.c. per pound (0.5 kg.) of body weight is given subcutaneously and 10 c.c. per pound (0.5 kg.) is given intravenously. Concomitantly, continuous infusions both intravenously and subcutaneously may be given. Ten per cent glucose must be given then only intermittently as it has a tendency to cause thrombosis in the vein at the site of the needle. When a continuous intravenous infusion is running, 5 to 8 c.c. per pound (0.5 kg.) per hour may be given when the infant is dehydrated. After that a rate of about 2 to 3 c.c. per pound (0.5 kg.) per hour is advised. The rate of introduction of fluids by the subcutaneous route depends on the patient's ability to absorb the fluid. A two-way hypodermoclysis set in which insertion of a "Y" tube in the tubing allows the fluid to be given simultaneously in two sites is desirable. It is unwise to allow a hypodermoclysis needle to remain in place more than twenty-four hours since it may lead to formation of an abscess.

In some cases of mild or moderately dehydrated infants and children a hypodermoclysis is sufficient to hydrate the patient. Any of the previously mentioned fluids may be given subcutaneously except 10 per cent glucose and 5 per cent sodium bicarbonate.

All of the fluids aid in restoring total fluid balance. The isotonic saline and Ringer's solution aid in restoring the electrolyte volume. The  $\frac{1}{6}$  molar sodium lactate and sodium bicarbonate aid directly in combating acidosis. The dextrose solution (5 per cent) and saline solutions aid indirectly in combating acidosis. The dextrose is par-



ticularly useful in correcting the ketosis of starvation. One should be sure, particularly after the patient has been hydrated, that an excess of saline is not given. Edema has been observed under such circumstances.

Citrated whole blood and plasma are useful and often necessary therapeutic additions. They should be given only after the patient first has been hydrated. Infants who weigh up to 10 pounds (4.5 kg) may be given 10 c c per pound (0.5 kg) of body weight. The condition of the patient, the degree of anemia and the degree of hypoproteinemia determine the amounts to be used and whether blood or plasma should be administered. For children from two to four years of age, a pint (500 c c) often is divided into three transfusions to be given on successive days.

The parenteral administration of amino acids has been a definite step forward in parenteral therapy. Hartmann suggested the use of a solution of equal parts of 10 per cent amigen (enzymatic hydrolysate of casein), 10 per cent dextrose and Ringer-lactate solution for subcutaneous or intravenous infusions. Space does not permit further discussion of the use of this material.

In the specific diarrheas sulfaguanidine or sulfasuxidine is given by mouth. The daily dose of these drugs is 2 to 4 grains (0.13 to 0.26 gm) per pound (0.5 kg) of body weight, given in divided doses every four hours. In the nonspecific diarrheas these sulfa drugs also are sometimes useful. A 5 per cent solution of sodium sulfadiazine given subcutaneously may be more valuable. The dose is  $\frac{3}{4}$  to 1 grain (0.05 to 0.065 gm) per pound (0.5 kg) of body weight.

Camphorated tincture of opium (paregoric) frequently is employed, probably more often than is necessary. The dose varies from 5 drops for a six months' old infant to 1 teaspoonful (4 c c) for a five year old child. The dose may be repeated every four hours if tolerated. Fresh tincture of iodine (U S P) in 1 to 2 ounces (30 to 60 c c) of water, grapefruit juice or grape juice has been helpful. The dose varies from 2 drops for an infant eighteen months of age to 10 drops for a child fourteen years of age, given three times daily. In cases of mild diarrhea, pectin-kaolin mixtures in teaspoonful doses three or more times daily are valuable.

## POISONS

Poisons ingested by children cause damage from either direct action on the gastro-intestinal tract or from the effects produced after the substance has been absorbed.

The most important substances causing damage by direct action are lye, sulfuric acid and lactic acid. If lye is ingested the mouth should be irrigated thoroughly with weak vinegar or lemon juice. The child also should be encouraged to swallow a quantity of this. If an acid solution has been ingested, a 5 per cent solution of sodium bicarbonate should

be used to irrigate the mouth. The patient also should swallow some of this solution. Children who have ingested carbolic acid, lysol (compound solution of cresol) or creosol should have the stomach washed out with large amounts of olive oil or warm water, about 5 ounces (150 c.c.) of olive oil is left in the stomach. If lavaging is not possible, the child should be encouraged to drink 5 to 6 ounces (150 to 180 c.c.) of olive oil. Large amounts of normal saline should be administered by all available routes. The use of dilating instruments should be left to those qualified in their use. Some physicians advise immediate attempts at dilatation and others recommend postponement of this procedure until the initial inflammatory process has completely subsided. At the Clinic we try to have the patient swallow a thread as soon after the burn as possible. Dilatations using the thread as a guide are then not attempted until the acute inflammatory process has subsided.

The other substances which may be swallowed by children are numberless. The introduction of new products for a variety of uses about the home increases each year the number of materials that may be ingested. It is impossible here to do more than suggest a few general principles for use when a situation such as this is encountered. 1. The stomach should be washed out unless the ingested substance is known to be harmless in the quantity ingested. Normal saline or tap water may be used as the irrigating solution. A charcoal suspension may be left in the stomach. 2. When the poison ingested is unknown a universal antidote composed of pulverized charcoal (2 parts), magnesium oxide (1 part) and tannic acid (1 part) may be given. The dose is 4 c.c. (1 teaspoonful) in a small glass of warm water. 3. If metals such as arsenic, lead or mercury are ingested, an irrigating solution of sodium thiosulfate, 15 gm. in 2 liters of water, should be used. If phosphorus has been ingested, oil should not be given as this increases the speed of absorption. The best antidote is a weak solution of copper sulfate. 4. If convulsions are present, lavage should be avoided. 5. Shock, convulsions, respiratory or circulatory failure, pain and other symptoms must be treated as they develop. Sedatives or stimulants may have to be given rectally, intravenously or intramuscularly. An anesthetic agent may be required to control severe convulsions.

#### REFERENCE

1. Hartmann A. F. Parenteral administration of amino acids. *J. Pediat.* 26 193-195 (Feb.) 1945.

# NONSURGICAL NEUROLOGIC EMERGENCIES IN CHILDREN

HADDOW M KEITH

SINCE the nervous system frequently is intimately concerned in severe and acute disease, so-called neurologic emergencies are numerous and of great variety. This paper is an attempt to present a number of the more common conditions involving mainly the nervous system of the child and requiring early diagnosis and immediate treatment. All these conditions will not be discussed exhaustively and consequently information concerning the technic of surgical treatment must be sought elsewhere. Some conditions will be discussed in different categories since at times it is necessary to deal with symptoms rather than recognized disease processes. The most common neurologic emergencies have been divided into five groups and will be discussed in the approximate order of frequency as follows: (1) convulsion, (2) head injury, (3) coma, (4) infection and (5) poisoning.

## CONVULSION

**Etiology**—The causes of convulsion are many. Most of them are included in the following list:

Acute infectious disease	Intracranial abscess
Brain tumor	Intracranial hemorrhage
Congenital cerebral defect	Meningitis
Congenital syphilis	Strychnine poisoning
Direct trauma	Tetanus
Epilepsy	Tetany
Gastro-enteritis	Uremia
Hydrocephalus	

**General Emergency Treatment**—In spite of the fact that one or more of the foregoing causes may be present and the fact that a correct diagnosis is essential before effective treatment can be instituted, convulsion frequently must be treated as an emergency. It is usually difficult to stop an individual convulsion but a series of convulsions may be treated effectively by medical or physical agents. As a rule, a general anesthetic agent produces the best results, and since ether is usually readily available and its action is well known, this is the agent of choice. The barbiturates, which may be given intravenously, subcutaneously or rectally, are also satisfactory.

Pentothal sodium [sodium 5-ethyl-5-(1-methyl-butyl) thiobarbiturate] is used intravenously for immediate effect. As a rule, this drug is not given to children less than ten years of age in connection with operations, however, in an emergency it may be given to young children in small doses, beginning with 1 c c of a 2.5 per cent solu-

tion and giving 0.5 to 1 c.c. at intervals of ten to fifteen seconds until the convulsion is controlled. At the same time the rectal administration of pentobarbital sodium,  $\frac{1}{2}$  to 3 grains (0.032 to 0.2 gm.), is begun. This medication should be repeated at intervals frequent enough to prevent further attacks until the underlying causative condition has been corrected and there is no likelihood of further attacks.

Sodium amytal (sodium isoamylcetylbarbiturate) has been used intravenously in a 5 per cent solution (5 mg. per kilogram of body weight) at a rate not exceeding 1 c.c. per minute. Its action is somewhat slower than that of pentothal sodium and its effect is more prolonged.

The rectal administration of avertin fluid (tribromoethanol) in the usual basic anesthetic dose of 75 mg. per kilogram of body weight, also has been effective in controlling a series of convulsions. This is supplied in amylene hydrate so that 1 c.c. contains 1 gm. of avertin and 0.5 gm. of amylene hydrate.

Another effective agent for rectal administration is chloral hydrate. This may be given every two to four hours in doses of 3 to 15 grains (0.2 to 1 gm.) depending on the age of the patient.

At times magnesium sulfate has been effective, especially in the control of convulsions caused by acute nephritis. This medication is administered intramuscularly in a 10 or 25 per cent solution (0.2 gm. per kilogram of body weight) and is repeated every four to six hours if necessary.

Oxygen given by means of a tent or mask is sometimes effective in controlling a series of convulsions, particularly if cyanosis is present. It may be used in conjunction with any of the previously described medications.

In certain cases, lumbar puncture with drainage of a few cubic centimeters of spinal fluid may also be beneficial but there is some danger in this procedure if there is increased intracranial pressure.

In certain conditions some measures are more efficacious than others and in some conditions specific measures are necessary. The most important points in treatment are discussed under the various causes of convulsion.

**Acute Infectious Disease**—Convulsions commonly occur at the onset of an infectious disease among young children. Since such an attack may be dependent on high fever, measures to reduce the temperature, followed by specific treatment if possible, should be undertaken. The administration of an enema using cold tap water or even ice water is of considerable help. After this the body may be sponged with tepid water, or a tepid pack may be applied. These measures may be followed by the administration of acetylsalicylic acid. The administration of anticonvulsant drugs usually is unnecessary unless a series of convulsions occurs.

**Brain Tumor**—Relief of pressure by operation is imperative when

brain tumor is present. Tumor of the brain is a relatively uncommon cause of convulsion but the pediatrician should keep in mind the cardinal symptoms and signs, that is, headache, vomiting, ataxia, swelling of the optic disks and roentgenologic evidence of increased intracranial pressure such as separation of sutures and dilatations in the skull.

**Congenital Cerebral Defect**—General anticonvulsant measures are useful. No treatment of the underlying cause is possible.

**Congenital Syphilis**—General measures, as previously outlined, followed by antiluetic treatment, should be instituted for convulsions caused by congenital syphilis. This condition is rarely encountered at the Clinic.

**Direct Trauma**.—In cases of concussion only, with no evidence of fracture, hemorrhage or laceration, general measures for control of convulsion may be used. Direct trauma is essentially a surgical condition.

**Epilepsy**—The single convulsion of grand mal, which is relatively short in duration, usually cannot be stopped once it has started. When status epilepticus occurs, most of the general procedures for treatment of convulsions are effective, either alone or in combination.

**Gastro-enteritis**—The fever or toxicity that is associated with gastro-enteritis probably is the precipitating factor in convulsion. Treatment is the same as for convulsion caused by acute infectious disease. Since dehydration is usually present, adequate amounts of fluid should be supplied.

**Hydrocephalus**—The diagnosis is dependent on abnormal enlargement of the head, with demonstration of an excessive amount of cerebrospinal fluid and enlargement of the ventricles. In external hydrocephalus the enlargement is due to fluid outside the ventricles. Convulsions caused by either internal or external hydrocephalus should be treated by general measures, followed by surgical treatment of the underlying condition if possible.

**Intracranial Abscess**—Diagnosis of intracranial abscess is usually difficult. The presence of such a condition is suggested by evidence of infection and of focal involvement of the nervous system. Treatment consists of general measures to control the seizures, followed by surgical treatment of the abscess.

**Intracranial Hemorrhage**—Convulsion, either focal or general in type, may be the result of hemorrhage due to injury at birth or to any gross injury of the head. If the bleeding is due to birth injury, chloral hydrate in doses of 1 to 3 grains (0.065 to 0.2 gm) by mouth or by rectum or pentobarbital sodium,  $\frac{1}{4}$  to  $\frac{1}{2}$  grain (0.016 to 0.032 gm), by rectum may be tried. Magnesium sulfate administered intramuscularly also has been satisfactory.

If the fontanelle is tense, spinal drainage may be indicated. Objections to this procedure have been raised on the basis of the fact that it dis-

turbs the patient and the lowering of the intracranial pressure may increase the tendency to hemorrhage. The administration of oxygen by use of a tent frequently is indicated. Menadione, 1 mg daily for seven to ten days, should be given intramuscularly.

If the hemorrhage is due to direct trauma, particularly if the middle meningeal artery is ruptured, surgical treatment is indicated.

**Meningitis**—Convulsion due to meningitis requires immediate treatment by general measures, followed by active treatment of the meningitis. This subject is discussed in the section concerning coma.

**Strychnine Poisoning**—Because of the prevalence in homes of preparations containing strychnine, convulsions due to this drug are not an uncommon occurrence. In spite of all precautions, children obtain and take these remedies and generalized seizures rapidly develop. The diagnosis usually is suggested by the history of swallowing excessive amounts of either a tonic or pills and the subsequent occurrence of generalized tonic convulsive seizures. The following immediate treatment, in the order given, has been effective: (1) pentothal sodium administered intravenously, as previously described, (2) insertion of a tracheal catheter to overcome the laryngeal spasm, followed by the administration of oxygen by use of a mask or tent and (3) pentobarbital sodium,  $1\frac{1}{2}$  to 3 grains (0.1 to 0.2 gm), given by rectum. This amount should be repeated frequently enough to prevent further convulsions for twelve to twenty-four hours or until danger of further convulsions is over.

Convulsions as well as other neurologic emergencies in children, may be due to many different poisons. Because of the extensiveness of the subject of poisoning it will not be discussed further in this paper and the reader is referred to other works for further information.

**Tetanus**—In our experience at the Clinic, convulsion due to tetanus has been infrequent in occurrence. The use of prophylactic antitoxin in cases of contaminated wounds undoubtedly has been a major factor in reducing the incidence to a minimum. In addition, active immunity may be produced by the use of tetanus toxoid, this method has been reported as satisfactory in Army practice. However, when convulsions occur suddenly and without obvious cause, the possibility of tetanus must be considered, and a search for a focus of infection, however small, should be made.

The paroxysms may be initiated by any stimulus, however slight. Such stimuli include sounds, sights, attempts at voluntary movement, and even light touch or pressure at any point.

The character of the convulsion caused by tetanus is rather distinct. There is preceding stiffness of the neck and jaw, with difficulty in swallowing. The convulsive attack is really a spasm in which the patient is in the opisthotonoid position with the body completely rigid and the head retracted. The face has a fixed expression, with firm contraction of the muscles of the jaw. There may be a single attack last-

ing only a few seconds, or attacks may occur constantly so that the patient is in almost continuous convulsions. The respiratory mechanism may become involved so that breathing is impossible.

In treating such a patient, all stimuli must be reduced to a minimum. The child must be kept in bed in a darkened room and handled as little as possible. Feeding may be carried out by means of a nasal tube, and glucose and saline may be given intravenously by continuous drip.

Avertin with amylene hydrate has been found effective in controlling convulsions caused by tetanus. The usual anesthetic dose (75 mg per kilogram of body weight) may be given rectally, followed at intervals of one to three hours by further administration of 10 to 15 mg per kilogram of body weight.

Sodium amytal may be given intravenously, and pentobarbital sodium also may be used. Use of these drugs is described under general emergency treatment.

Curare (intocostin)\* also has been used intramuscularly and intravenously. Cullen and Quinn<sup>5</sup> gave approximately 0.05 gm every three hours to an adult male. This dose is approximately 0.0008 per kilogram of body weight. It should be used in sufficient amount and often enough to relieve the pain and muscular spasm.

A large amount of antitoxin should be given as early as possible after the occurrence of convulsion due to tetanus. Calvin<sup>2</sup> advised the intravenous injection of 50,000 units of antitoxin as follows: Test patient for sensitivity to horse serum, then dilute the serum in 500 c c of physiologic saline at body temperature and give intravenously at the rate of 60 drops per minute. If chill occurs, stop the intravenous injection and give the remainder of the serum intramuscularly. In addition, give another 50,000 units intramuscularly. Holt and McIntosh<sup>8</sup> advised that the primary wound be excised and antitoxin given no matter how much antitoxin previously had been administered.

To, any—Convulsion in infants and small children who are less than three years of age is sometimes caused by tetany, usually associated with some degree of rickets. Such a seizure is particularly dependent on a low level of calcium, many patients having less than 8 mg per 100 c c of serum. Chvostek's sign is present. This consists of increased irritability of the peripheral nerves as noted by clonic contractions of the facial muscles of one side when the seventh nerve is lightly tapped. Further evidence of the presence of tetany is obtained by Trousseau's sign, that is, the tetanoid position of the hand when firm circular pressure is made about the upper arm.

Convulsions due to tetany may be generalized and may be indistinguishable from convulsions due to other causes. They may be controlled by one of the following methods. Calcium gluconate in 10 per cent solution may be given intravenously or intramuscularly, in 10 c c doses every four to six hours. Sloughing occasionally may oc-

\* Prepared by E. R. Squibb & Sons, New York City

cur after intramuscular injection. Calcium chloride may be given by mouth or in extreme cases by vein. The latter method must be used with care since injection of the solution outside a vein may cause sloughing. When calcium chloride is given orally the initial dose is 45 to 60 grains (3 to 4 gm) in 10 per cent solution in water or milk. This is followed by a dose of 15 grains (1 gm) three or four times daily. Twenty-four hours after calcium therapy has been started cod liver oil or other vitamin D preparation should be given and continued indefinitely. Chloral hydrate may be given orally or rectally. Three to 5 grains (0.2 to 0.3 gm) may be given to infants less than six months of age and 5 to 10 grains (0.3 to 0.65 gm) to children more than six months of age. In some cases of convulsion, the administration of ether may be required.

**Uremia**—Uremia, or pseudo-uremia in the course of nephritis may precipitate convulsions. When the blood pressure is elevated, uremia may develop regardless of whether the retention of nitrogen is excessive. Under such circumstances drowsiness or vomiting with the onset of coma, may be accompanied by generalized convulsive attacks.

Uremic convulsions may be treated by any of the methods previously outlined under emergency treatment. Lumbar puncture is one of the methods of choice. Some authors recommend, in addition the use of morphine. Magnesium sulfate in 2 per cent solution should be injected intravenously not faster than 2 c.c. a minute, until the blood pressure returns to normal. After the convulsions have ceased and the patient is no longer in a state of coma, large doses of a saturated solution of magnesium sulfate should be given by mouth until the blood pressure is stabilized. The patient should be urged to take fluids in large amounts.

#### HEAD INJURY

Children frequently receive injuries to the head. Most of these cases must be considered as of an emergency nature. The lesions may be the result of birth trauma with or without hemorrhage or of trauma from external causes with or without hemorrhage. The injury may or may not be associated with fracture or loss of consciousness. In many cases surgical treatment, which is beyond the scope of this discussion, is necessary.

**Head Injury without Loss of Consciousness**—The parents should be informed that the child may become pale, may vomit once or several times and may be unusually quiet for several hours. Although these symptoms are not of grave import, if increasing drowsiness is noted, immediate medical or surgical attention is necessary. Hematomas and lacerations necessitate surgical treatment. The patient should be at rest in bed until a day or two after these symptoms have disappeared.

**Head Injury with Concussion**—The patient must be kept absolutely at rest in bed in the horizontal position for from several days to sev-



eral weeks, depending on the signs and symptoms. Frequent observations of the pulse rate, temperature, respirations and blood pressure are of great importance. Shock must be treated immediately with transfusion of blood, plasma or serum albumin or infusion of glucose and saline. Scalp wounds, hemorrhage and fractures of the skull require surgical consideration and treatment. A gradual rise in intracranial pressure over a period of some hours also indicates the necessity for surgical consultation. If unconsciousness persists, feeding by tube may be necessary.

**Head Injury with Hemorrhage**—Surgical treatment, in addition to general measures, usually is indicated in cases of head injury with hemorrhage. Lumbar puncture is contraindicated since it may increase the bleeding. Craig<sup>4</sup> recently stated that in both open and closed injuries anoxia should be prevented by insuring free passage of air for adequate breathing and by administering oxygen. He also pointed out that the sulfonamides and penicillin "have so reduced the incidence of infection that the scope of surgical treatment has been immeasurably increased."

Hemorrhage due to rupture of the middle meningeal artery with the formation of subdural hematoma always requires emergency treatment. There is a history of trauma with or without loss of consciousness. If the patient is unconscious, he subsequently may become conscious for a half to one hour and then gradually become increasingly drowsy with headache or vomiting and slowing of the pulse rate. In addition, there are focal neurologic signs, such as a dilated pupil on the side of the hematoma and positive Babinski and Chaddock reflexes on the opposite side. Roentgenograms reveal fracture of the skull. As soon as the diagnosis is made, treatment is entirely surgical.

#### COMA

Coma, which is only a sign of an underlying disease or injury, is often encountered, particularly in hospital practice. Determination of the etiology is of prime importance, since treatment depends almost entirely on the cause. The many common causes of coma include head injury, brain tumor, meningitis, pyogenic and tuberculous infection, acute encephalitis, diabetes, uremia, acute infectious diseases, poisons, intracranial hemorrhage and status epilepticus. Several of these conditions are discussed elsewhere in this paper. Some of the rarer causes of coma are narcolepsy, cerebral embolism, thrombosis and hepatic insufficiency.

**Brain Tumor**—In many cases of tumor of the brain there is a history of weeks or months of vomiting and headache frequently associated with muscular weakness, ataxia and perhaps increasing drowsiness or lassitude. Examination usually reveals evidences of increased intracranial pressure, such as papilledema, and roentgenographic evidence of separation of the cranial sutures. Detailed neurologic examination

may reveal focal signs which give a clew to the site of the tumor. Surgical treatment usually is indicated. If this is not feasible, roentgen treatment may give palliative relief.

**Diabetes**—Coma caused by diabetes mellitus is primarily a metabolic and not a neurologic problem. A history of diabetes mellitus may or may not be obtained. Glycosuria, acetonuria and hyperglycemia usually are demonstrable, as well as a low content of carbon dioxide in the plasma. In cases of coma due to an overdose of insulin these findings are not present and the history of administration of insulin plus hypoglycemia gives the clew to diagnosis. Treatment of diabetic coma requires skill, close observation and laboratory facilities such as are found in a well-equipped hospital and preferably should be undertaken only when these conditions are fulfilled.

**Encephalitis (Acute)**—This subject is discussed subsequently under the heading of infection.

**Head Injury**—The diagnosis of coma due to an injury to the head usually is indicated by the history of trauma or by the obvious evidences of direct injury. In occasional cases no history is available. A careful examination of the head, including roentgenograms, may indicate the site of the trauma. Treatment of such a condition is outlined in a preceding section concerning convulsion due to direct trauma.

**Meningitis (Pyogenic and Tuberculous)**—In cases of pyogenic meningitis, evidence of acute infection, such as fever possibly with headache, convulsion and elevation of the leukocyte count, is present. These symptoms and signs are accompanied by nuchal rigidity and, as a rule, Kernig's sign. The patient may lie with the head retracted and may have considerable general rigidity of the muscles. The spinal fluid usually is under increased pressure and contains large numbers of leukocytes and an abnormal amount of protein. On direct examination of the fluid, organisms may be present, or may be cultured on the usual media. Treatment is outlined under a subsequent section concerning infection.

In cases of tuberculous meningitis, the onset is usually more gradual than in cases of pyogenic meningitis, with change in personality, increased irritability, fretfulness, headache in older children, anorexia and sometimes unexplained vomiting. The acute onset of symptoms such as convulsion or coma, which occur in infants requires emergency treatment. The pressure of the spinal fluid may be considerably increased. It is clear or faintly cloudy and contains mainly lymphocytes, from 25 cells to several hundred cells per cubic millimeter. Occasionally neutrophils predominate. The content of protein is moderately elevated, and the amount of chlorides and sugar is reduced. Tubercle bacilli usually may be found in the fluid, especially in the fibrous pellicle which often forms on allowing the fluid to stand for some hours. Organisms also may be demonstrated by staining a cover-

slip which has been placed for twelve hours or so in the bottom of a glass cell containing spinal fluid

There is no satisfactory treatment for tuberculous meningitis. Convulsions should be treated as outlined under emergency treatment. The newer drugs, such as promizole (4, 2'-diaminophenyl-5' thiazole-sulfone), have given some therapeutic promise but they are still in the experimental stage.

**Uremia**—This condition, which also is primarily a metabolic disturbance, is discussed in detail in another paper<sup>9</sup> in this issue.

**Unusual Conditions**—Among the rarer causes of coma and similar states in children may be mentioned narcolepsy, cerebral thrombosis or embolism, and hepatic insufficiency.

*Narcolepsy* may not be considered as true coma but older children occasionally may be found in an unconscious state during an attack. No immediate treatment is required but benzedrine sulfate (amphetamine sulfate) or ephedrine have been found of considerable value in preventing the recurrence of attacks of somnolence.

*Cerebral thrombosis or embolism* is rare in childhood. The former may occur in the larger veins or sinuses in cases of acute infectious disease or of sepsis and dehydration in infants. The most common is thrombosis of a lateral sinus, associated with otitis and mastoiditis. This is essentially an otologic condition and the treatment is surgical. Cavernous sinus thrombosis is discussed in the following section concerning infection.

Coma, maniacal states and even convulsions may occur in *hepatic insufficiency*. A trial of treatment with glucose in 10 per cent solution, with or without insulin, may tide the patient over such a difficulty.

## INFECTION

**Cavernous Sinus Thrombosis**—This severe and often fatal condition may occur as an emergency. It usually takes the form of thrombophlebitis, which at first may be unilateral but later may become bilateral. There is usually a source of infection about the upper portion of the face or in the nose, and infection of the blood stream is frequently present, the organism being staphylococcus or streptococcus. The patient complains of headache or pain in the forehead, about or behind the eye. There also may be pain in the teeth on one side. The general reaction is severe enough at times to cause delirium.

The physical signs consist of edema of the eyelids, exophthalmos or severe proptosis, ptosis, chemosis and weakness of the various extraocular muscles. Papilledema and engorgement of the retinal veins also may be present. The spinal fluid may be cloudy and contain many leukocytes.

Prior to the advent of treatment with the sulfonamide compounds and penicillin, management was ineffective. Recently recoveries have

occurred following the use of these preparations, with or without heparin.

Cohen and Cohen,<sup>8</sup> in 1942, reported the successful treatment of a two year old child following the administration of sulfathiazole orally and intravenously, heparin and *Staphylococcus aureus* antitoxin. Edelson,<sup>9</sup> in 1944, reported the recovery of one patient after the use of sulfathiazole, sulfadiazine and heparin. Goodhill<sup>7</sup> reported one case and Wiesenfeld and Phillips<sup>10</sup> also reported a case in which favorable results followed treatment with penicillin and heparin or with penicillin alone. In both cases large doses of penicillin were administered, a total of approximately 1,000,000 Oxford units being given to a five year old child, and 2,000,000 to a young adult. The larger part of the penicillin was given intravenously in amounts of 50,000 to 150,000 units daily.

**Encephalitis (Acute).**—The occurrence of convulsions or coma as a result of acute encephalitis may require emergency treatment. There are many varieties of encephalitis, the most definite types being epidemic encephalitis, acute polioencephalitis, encephalitis following vaccination, encephalitis complicating acute infectious diseases and encephalitis due to poisons such as lead or arsenic. A rather rare form, toxoplasmosis, may occur in early infancy and may be of congenital origin.

Such patients usually have high fever, delirium, convulsions or coma and there may be signs of meningeal irritation. Ataxia may be pronounced, asphyxia may develop or signs of lesions of one or more of the cranial nerves may be present. The prognosis is poor except in the postinfectious types of encephalitis. If the patient survives, there are frequently residual symptoms such as mental disturbances, paresis or paralysis.

Treatment is not of a specific type but is essentially symptomatic. Lumbar puncture and the use of anticonvulsants or sedatives are indicated, as discussed earlier in this paper in the section concerning convulsions. Hot packs or baths also may be employed. Food and fluids may be given by gavage, and fluids alone by parenteral injection. If retention of urine occurs, catheterization is necessary.

**Intracranial Abscess.**—An intracranial abscess may require emergency treatment due to extension from acute mastoiditis or sinusitis. Such a patient may have alarming symptoms such as aphasia, hemiplegia, delirium or coma. There is usually a history of infection of the middle ear, mastoid or sinuses with elevated temperature, increased leukocyte count, physical signs of meningitis and evidence of acute meningitis on examination of the spinal fluid.

Treatment, which is essentially surgical, consists of evacuation or aspiration of the abscess. Sulfonamide compounds or penicillin or both also should be administered.

**Meningitis (Acute).**—This condition at times requires emergency

treatment because of its sudden onset, with or without convulsion or coma. The important diagnostic criteria are outlined in a preceding section. Treatment consists of control of convulsions, if present, and of the meningitis. Treatment depends to some extent on the type of infecting organism, but at the present time it consists primarily of use of one of the sulfonamide compounds or penicillin or both. Sulfadiazine usually is the sulfonamide compound of choice at the present time. It can be given intravenously, subcutaneously or orally in such amount that the level of the drug in the blood is above 15 mg per 100 c c. It is advisable also to give enough sodium bicarbonate to keep the urine alkaline. The penicillin may be given intravenously by continuous drip, intrathecally or intramuscularly, giving 80,000 Oxford units daily, 10,000 units every three hours.

Anti-influenzal rabbit serum has been advised in cases of influenzal meningitis in addition to the use of sulfadiazine. Alexander<sup>1</sup> recommended that it be given about twelve hours after beginning sulfadiazine in amounts of 100 to 150 mg of antibody nitrogen if the sugar in the spinal fluid is less than 15 mg per 100 c c. If the spinal fluid sugar is between 12 and 25 mg, 75 mg of antibody nitrogen should be given, if it is between 25 and 40, 50 mg, and if more than 40, 25 mg.

Tuberculous meningitis, which requires emergency treatment only if convulsions or sudden coma develop, is discussed in a preceding section concerning coma.

**Tetanus**—Information concerning this subject is given under convulsion.

#### REFERENCES

- 1 Alexander, Hattie E. Treatment of type B hemophilus influenzae meningitis. *J Pediat.* 25 517-532 (Dec) 1944
- 2 Calvin, J K. Tetanus—its prevention and treatment. *New York State J Med* 41 1636-1640 (Aug 15) 1941
- 3 Cohen, Morris and Cohen, H J. Septic thrombophlebitis of the cavernous sinus in a two year old child, with recovery. *Am J Dis Child* 63 546-551 (Mar) 1942
- 4 Craig, W McK. Injuries to the central nervous system. *Proc Inst Med Chicago* 15 223-224 (Jan 15) 1945
- 5 Cullen, S C and Quinn, C S. Use of curare in treatment of tetanus, case report. *Surgery* 14 256-260 (Aug) 1943
- 6 Edelson, David. Staphylococcic thrombophlebitis of the cavernous sinus, report of a case with recovery with chemotherapy and heparin. *Arch Ophthalmol* 31 329-330 (Apr) 1944
- 7 Goodhill, Victor. Penicillin treatment of cavernous sinus thrombosis. *J.A.M.A.* 125 28-30 (May 6) 1944
- 8 Holt, L E., Jr and McIntosh, Austin. *Holt's diseases of infancy and childhood*, a textbook for the use of students and practitioners. Ed 11, New York, D Appleton-Century Company, 1940, 1421 pp.
- 9 Kennedy, R L J. Management of nonsurgical emergencies associated with the urinary tract of children. *M CLIN NORTH AMERICA* 29 874-877 (July) 1945
- 10 Wiesenfeld, I H and Phillips, Edward. Thrombophlebitis of a cavernous sinus following extraction of teeth, cure with penicillin and heparin. *Arch Otolaryng* 40 497-500 (Dec) 1944

## CLINICS ON OTHER SUBJECTS

---

### POSTWAR ASPECTS OF SOME TROPICAL DISEASES

GEORGE G. STILWELL

At the present time there is considerable discussion throughout the United States concerning the possibility of a great postwar increase in the incidence of tropical diseases both in the returning armed forces and in the civilian population. There is also speculation about whether new diseases not heretofore present in this country will be imported, and in such event, if the proper vectors are present, whether such new diseases will establish footholds and spread throughout areas which are suitable for the propagation of these diseases.

No doubt the practicing physician will see many more cases of so called tropical diseases in the next decade or two than he has encountered in his past experience, and his diagnostic acumen often will be taxed by the bizarre clinical pictures which some of these unfamiliar disease entities will present. In recognition of this probability, there has been considerable acceleration during the last two years in the teaching program of tropical medicine from the standpoint of both the clinician and the laboratory diagnostician. This is evident in the greatly expanded departments of tropical medicine in both the Army and the Navy Medical Corps. The medical schools of North America also have felt the effect of this increased emphasis on thorough training in tropical diseases, and a plan for improvement of the teaching of tropical medicine in the medical schools of the United States and Canada has been developed through co-operation of the Association of American Medical Colleges, the Office of the Surgeon General of the United States Army, the National Research Council, the Army Medical School and Tulane University. This plan is being aided financially by the John and Mary R. Markle Foundation.

Various aspects of this problem have been studied by specialized workers in tropical diseases and by leaders in the field of public health. The conclusion drawn from these studies is that the return to this country of many diseased members of the armed forces presents definite potential dangers to the health of the nation. It is also the consensus that the importance of these potential dangers perhaps has been overemphasized in the mind of the average physician. It is evident that the Army, the Navy, and the public health authorities are fully aware of all the possibilities inherent in the forthcoming situation, and that these agents together with a medical profession better trained in tropical medicine, will be able to cope with any developments which might ensue.

The importance of this problem as related to the general population of our country warrants a brief discussion of some of the more

important of these potentially dangerous diseases Particular emphasis should be placed on an attempt to anticipate what may be the future course in the United States of the diseases which are imported by our returned fighting men It is plainly evident that our soldiers and sailors are being exposed to more diseases in the present global conflict than they have been at any other time in history, and it is a foregone conclusion that they will bring some of these diseases home with them

Several important factors concerned in the method of spread of these diseases should be considered before the individual disease entities are discussed The acute diseases, which have a comparatively short period of incubation and communicability, are less likely to be introduced to this country than those diseases that are of a chronic nature or that possess a long incubation period Those diseases which require for their propagation a specific intermediate host may be imported into this country but they cannot become established as endemic foci unless there is already present this specific intermediate host It is possible that in these cases the specific host also may be introduced and may thrive in some sections of the United States There may be a greatly increased number of asymptomatic carriers of certain diseases returning to this country when demobilization occurs It is possible that new and much more pathogenic strains of organisms may be imported which will produce disease of heightened severity in the civilian population Finally, some diseases which are at present localized in comparatively small areas in this country may be much more widely distributed by the return of men from these endemic areas to their homes

#### ACUTE DISEASES

The group of acute diseases by virtue of their short incubation period probably will not present any particularly grave postwar menace to civilian health

The first of such acute diseases is *yellow fever*, whose etiologic agent is a virus Yellow fever may be considered to be a historical curiosity here in the United States because it was last seen in 1905 in New Orleans Without eternal vigilance, however, another introduction of this disease is possible As far as geographic distances are concerned, we are farther away from yellow fever than ever before because it is now absent from Mexico, the West Indies, and the upper part of Central America If we use air travel time as a measure of distance, however, we are much nearer yellow fever than ever before because this infection is still found in Colombia, Venezuela, and some parts of Panama.

There appears to be little chance that members of the armed forces will introduce the virus to this country by returning from areas where yellow fever is endemic, while the disease is still in the incubation

period. This is because of the practice of universal vaccination against yellow fever of all personnel entering areas where the disease is endemic. By use of the mouse protection test, it has been found that yellow fever exists in new and vast areas where previously it has escaped detection. These areas are in Africa, where the endemic zone extends eastward more than 3,000 miles to the upper Nile, and in Brazil along the Amazon basin, together with important areas of Colombia and Venezuela. The discovery of yellow fever in the jungles of South America has emphasized the importance of vaccination as a means of prevention because the ordinarily effective measures of mosquito control that have been so successful against the vector of urban yellow fever; namely, the domestic *Aedes aegypti*, are powerless against yellow fever which occurs in the great expanses of almost uninhabited tropical forest.

In such areas vaccination is the best means available for protection against the disease. The vaccine in present use is a strain of living yellow fever virus which has been modified by prolonged passage through tissue cultures until it has lost much of its neurotropic and viscerotropic virulence. It still, however, retains considerable antigenic effectiveness. Many studies indicate that the immunity produced in most vaccinated individuals persists for at least four years. Effective protection may last even longer than this in view of the lifelong immunity conveyed by the disease itself.

The vaccine in its present state is as safe as any biologic agent containing virus can be. Before the present form of vaccine was available, small amounts of human serum were used in the manufacture to aid in preserving the virus. A form of hepatitis resembling catarrhal jaundice developed in many persons injected with the vaccine containing this human serum. After exhaustive study it was concluded that this hepatitis probably was due to some icterogenic agent, perhaps a virus, encountered occasionally in human serum and inadvertently introduced into the vaccine during its manufacture. In the newest type of vaccine, chick embryo juice is substituted for the human serum. During the last two years millions of injections of this serum-free vaccine have been administered and there have been no further reports of jaundice or other symptoms except slight fever and occasional malaise occurring about a week after injection.

The greatest danger of a possible postwar introduction of yellow fever is through the medium of air travel. Several measures are being used to control this danger and vigilance must be maintained if we are to avoid this menace. All persons traveling into endemic areas are urged to be vaccinated against yellow fever. Persons returning from endemic regions are given regular inspections by quarantine authorities. Their temperature is recorded. Anyone who shows signs of illness or an elevated temperature is detained pending a definite diagnosis. If a person is well but has not been vaccinated against vel-



low fever and possibly has been exposed to the disease, he is kept under observation at his destination by health officials until the six day incubation period is past. These latter precautions are not necessary if the destination is north of any areas where *Aedes aegypti* is found. Airplanes returning from areas where yellow fever occurs are thoroughly sprayed to kill all incoming insects.

The impression should not be gained that vaccination is a preventive agent which makes further mosquito control unnecessary. Extinction of *Aedes aegypti* is still the best method for control of yellow fever in cities and other accessible places in the tropics and subtropics. Because *Aedes aegypti* is primarily domestic in its habits it is quite accessible and therefore is particularly vulnerable to anti-mosquito measures. The efficacy of these measures has been proved in Brazil where in most cities and in many comparatively extensive areas *Aedes aegypti* can no longer be found.

Sawyer<sup>2</sup> has stated that there are three lines of defense against post-war introduction of yellow fever. The first line is vaccination and the elimination of the mosquito vector from seaports in endemic areas. The second line of defense may be regarded as the various quarantine procedures at our borders. The third line of defense is the eradication of *Aedes aegypti* wherever it exists in the United States. If these measures are taken, they are adequate to keep our communities non-infectable by yellow fever without resorting to general vaccination of the civilian population.

*Dengue fever* has the same mosquito vector, *Aedes aegypti*, as does yellow fever, and thus the problems of mosquito control are common to these two diseases. Dengue fever is already endemic in the American tropical and subtropical regions. It is important from a military standpoint as it may cause epidemics in the armed forces rendering troops temporarily unfit for active fighting. Because it has a short incubation period, the only danger of an extensive new introduction of it into the United States lies in the possible importation of the disease from Latin America. Until *Aedes aegypti* is eradicated from our southern states the danger of future epidemics remains a definite threat.

Among rickettsial diseases, one is to be feared above all during times when great masses of troops are engaged in conflict. That one is *louse-borne typhus fever*. We need not consider here the comparatively innocuous murine or flea-borne typhus fever, which has been endemic for years in the southern areas of the United States.

Louse-borne typhus is most prevalent in late winter and spring, and thus the cold weather present in the United States would not be a deterrent to its spread. The body louse is the vector concerned in this form of typhus. At the present time, except for slum areas, this insect is comparatively scarce in this country. Therefore, we should feel fairly secure against any extensive invasion of this type of typhus.

fever This security is further bolstered by the fact that modern de-lousing procedures in returning troops are much more efficient than in World War I

The tremendous efficacy of the newest insecticide, commonly known as DDT (1,1,1 trichlor-,2,2 diparachlorophenyl-ethane), is proving a vital factor in the present low rate of typhus, both in the armed forces and in the civilian populations with which they are mingling Thus it appears improbable that there is much danger of wholesale introduction of typhus fever into this country by our armed forces.

Another factor which will be of great importance in preventing postwar spread of this disease is the universal vaccination against typhus which is being performed on all military personnel who go to areas where they may possibly be exposed to typhus fever The efficacy of the type of typhus vaccine being used at present is evident in the practically complete absence of typhus fever in our troops in North Africa and Italy This freedom from typhus is even more remarkable when we consider that extensive epidemics of abnormally severe typhus have occurred in the natives of the African area within the last two years, and that many cases of typhus have developed in unvaccinated British troops living in the same localities as our vaccinated troops

The future situation in this country with respect to the danger of introduction of typhus to the civilian population appears quite safe if the occurrence of the body louse is kept controlled

Several other acute diseases may be briefly considered *Plague* should not be any more of a problem after the war than it is at present in the western states A vaccine is available for use in our troops abroad and it appears to be moderately effective There should be no new outbreak of plague unless there is some breakdown of our present efficient system of ship inspection which might allow new introduction of infected rats

*Phlebotomus fever*, or sandfly fever, is another disease which has occurred in a large number of troops It is of short duration, usually three or four days, but it is of military importance because the afflicted person is quite disabled for military action during its course It should not create any postwar problems because the *Phlebotomus* fly is found here in only a few small regions

*Cholera* has not been encountered to any great extent in the fighting men However in the event of a more extensive Burman and Indian campaign causing widespread native epidemics, the disease may appear in our men stationed in these areas A fairly efficient vaccine is available for prophylactic use in persons who are to enter zones where cholera is endemic The likelihood is extremely remote that any person could become a carrier of the *Vibrio* and bring it back to this country Thus we should not have any problems with this disease after peace comes

## CHRONIC DISEASES

Among the chronic diseases which might create postwar problems, first and foremost from the standpoint of military importance is *malaria*. The scope of this discussion does not permit full consideration of the diffuse manifestations of this problem, but a few of the more important aspects will be outlined.

It is obvious that large numbers of our troops are being infected with malaria, particularly those fighting in the South Pacific area and in Italy. In spite of proper treatment many relapses have occurred, and the disease may remain latent for many months. Suppressive treatment with atabrine tends to prevent the initial clinical appearance of malaria for periods as long as a year after infection. Thus it appears impossible to prevent the return to this country of large numbers of men infected with malaria.

The chief problems arising from the return of these malarious individuals from abroad may be summarized, according to McCoy,<sup>1</sup> as follows: 1. There is a possibility of establishing new endemic foci of disease in regions which are now free from malaria. 2. Importation of new strains of the parasite may occur in areas where the disease is already prevalent, with a resulting increase in the amount of malaria in these areas. 3. There must be prompt recognition and proper treatment of relapses occurring in soldiers returned to this country.

Much attention has been directed to the first of these problems, namely, the establishment of new endemic foci. Every section of the United States contains anopheline vectors capable of transmitting malaria. *Anopheles quadrimaculatus* is fairly numerous during the warm seasons in many areas which at present do not have malaria. This is especially true in such regions as the Upper Mississippi basin and the Hudson Valley.

One suggestion which has been made is to segregate for a certain period of time all personnel returning from malarious areas, especially if these men are to be sent to parts of the country where malaria is not present. This procedure is obviously impractical because relapses may occur after many months, during which time there has been no clinical or laboratory evidence of infection.

The past history of previous outbreaks of malaria in nonendemic areas of the United States would indicate that the potential dangers in allowing dispersion of these infected individuals are not particularly great. These outbreaks of malaria have consisted of only a few cases and have been characterized by a tendency to remain confined to small areas and a propensity for spontaneous subsidence even without added measures of mosquito control.

The second problem is the possibility of importation of new strains of malarial parasites. Clinical experience with infected troops in the South Pacific tends to indicate that the strains of malarial organisms being encountered there are quite different from those already en-

demic in the United States. These conclusions are drawn from the fact that the relapse rate is much higher in individuals acquiring malaria in the Pacific islands than it is in persons infected in the United States. This greatly increased relapse rate has occurred in spite of intensive treatment. Another bit of clinical evidence to strengthen this conclusion is the high rate of infection among American Negro troops. These colored troops have had the same rate of malarial infection as have the white troops living under the same combat conditions. This is in contrast to the condition existing in the southern part of the United States where Negroes appear to have considerable immunity to the malarial parasites found in this country.

There is a definite possibility that these more virulent strains will be imported into communities where the inhabitants have little or no natural immunity to these new parasites. However, the danger of this introduction resulting in any serious epidemic is remote. This is because most of the cases of relapsing malaria in our returning troops are due to *Plasmodium vivax*, the tertian type. The reason for the preponderance of this species in the relapsing cases is that it is more difficult to produce a permanent cure in this type of infection than in others. Malaria due to *Plasmodium vivax*, however, is not considered to be especially dangerous as a source of widespread disease in this country because experience in the past shows that serious epidemics of malaria are practically always due to *Plasmodium falciparum*, the subtertian or estivo-autumnal type. It is this latter type which predominates in the tropics.

The third problem, that of prompt recognition and treatment of malarial relapses, resolves itself primarily as a function of the private physician. Many physicians of the United States, particularly those in the northern sections, have had practically no experience with malaria from the diagnostic, therapeutic or public health aspects. If the physician fails to recognize cases of relapsing malaria, therapeutic measures may be delayed until the patient is in serious condition. Delay in therapy is especially hazardous to the patient suffering from estivo-autumnal malaria with cerebral involvement. The public health aspect of delayed recognition of these cases is important, as this delay will greatly aid in spreading the disease to other individuals. To counteract this gap in experience and knowledge, an extensive educational program is necessary to familiarize the physicians of this country with the protean manifestations of malaria and to keep them constantly aware of the possibility of these cases falling into their hands. After the war this situation will be alleviated considerably by the return of thousands of physicians who have had extensive experience in tropical diseases during their military services. These physicians undoubtedly will contribute greatly to increased efficiency in the practice of tropical medicine throughout the country.

*Filariasis* constitutes another chronic disease which is a vexing prob-

lem to the military medical personnel. The term "filariasis" in a broad sense includes several categories of parasitic nematode infestations. This discussion is limited to that form due to *Wuchereria bancrofti*. In this disease the adult worms live in the circulatory or lymphatic systems, the connective tissues or the serous cavities. The adults produce certain small larval forms, called microfilariae, which commonly invade the circulating blood or lymph spaces.

The seriousness of the filariasis problem lies in the fact that, while it does not cause large numbers of troops to become physically unfit for military duty, it does produce profound mental disturbances in the men affected with this disease. Thus the primary problem in filariasis is one of proper psychotherapy.

These important psychiatric problems arise because the men have seen in the native population horrible examples of long-standing and neglected cases of filariasis with extreme degrees of devastating elephantiasis and tremendously deforming scrotal involvement. Thousands of our troops have been living and fighting in hyperendemic areas of filarial disease, and a large number of these men have been infected with microfilariae. When the acute lymphangitis and lymphadenopathy associated with early filariasis develop, these men immediately conclude that their physical state ultimately will be the same as that of the natives they have seen. This naturally produces a profound sense of mental depression. Many write home to break engagements, fearing they will infect their future wives with the same disease. They write to their families saying they can never return home or lead normal lives because they have contracted a loathsome disease. These men tend to become chronic hospital invalids even though their physical condition may be steadily improving.

It is self evident then that the first and most important form of therapy is to change the mental attitude of these men. They must be reminded that the natives they have seen have lived under unhygienic conditions, and constantly have been reinfected with microfilariae over a period of many years. They must be reassured emphatically that since they have been removed from endemic areas no further infection will take place. They must be reassured constantly that probably no progressive or disfiguring elephantiasis or scrotal deformities will develop. Many hundreds of men who presumably have filariasis have been returned to this country. It is much better psychologically to keep these men in barracks and to refrain from hospitalizing them unless such a procedure is absolutely necessary. A series of graduated physical exercises is prescribed for them, and in the majority of cases the men are soon able to return to full duty. Many of them have married and the number of pregnancies normally expected has ensued from these marriages.

Continued observation of these patients indicates that the physical signs of disease are disappearing. Extensive lymphadenopathy has not been a prominent feature in the majority of cases. Clinical evidence

would lead to the conclusion that many of the adult worms are disintegrating. The diagnosis in the great majority of cases has been made on the history of exposure in a hyperendemic area with the subsequent development of lymphangitis and lymphadenopathy. Biopsies of acutely involved lymph nodes have been performed in a few cases and the adult worms have been identified. This procedure has been abandoned, however, as it leads to extensive inflammation in the lymphatics. As far as could be ascertained at the time of preparation of this paper, circulating microfilariae have not been found in the blood of any of these patients who have filariasis. It is true that in many of these instances the infection had not been present long enough to allow the demonstration of microfilariae in the blood stream. However, the complete absence of larval forms in the blood of every one of these patients, in spite of extensive search, adds another bit of evidence to support the conclusion that the disease will regress rather than progress in our returning men.

The possibility of filariasis again becoming established in the United States as a result of infection spread from our returning military personnel appears extremely remote. This is in spite of the fact that complete development of the larval forms of *Wuchereria bancrofti* has been observed in thirty-two different types of mosquitoes, and that *Culex fatigans*, the most common vector, is found in our country. For many years an endemic focus of filariasis existed at Charleston, South Carolina, and microfilariae could be found in an appreciable number of the inhabitants of this locality. At the present time this region is practically free from this disease. This focus of infection apparently arose from importation of slaves from Africa who were heavily infested with microfilariae. As a suitable mosquito vector was present, the disease continued to be active for many years, but because of improved general hygienic conditions and mosquito control measures the infestation gradually has died out.

It does not seem likely then that new endemic areas of filariasis will be set up in the United States in view of the fact that, up to the present time at least, there has been complete absence of microfilariae in the returned cases. If at a later date microfilariae do appear in these men it seems likely that the public health authorities with modern methods of mosquito control available will be able to prevent any spread to the general population.

*Bacillary dysentery* has been of some concern to members of our armed forces. Several epidemics have occurred in army camps in this country and in Africa. Fortunately, chemotherapy with sulfonamide drugs has proved extremely effective in curing the acute phases of the disease and there has not been a great amount of resulting military disability. Past experience with this disease tends to indicate that a certain proportion of patients who have active disease and also some of the asymptomatic carriers will harbor the organism for several years. Therefore, it is highly probable that new and more

potently virulent strains of the bacillus will be imported into the United States with returning troops. There is a possibility that these highly pathogenic strains might give rise to postwar epidemics, especially in institutions such as mental or convalescent hospitals, and in army camps. This potential hazard can be minimized by strict attention to maintaining efficient conditions of general sanitation and personal hygiene.

Another form of dysentery which is of military and civil importance is that caused by the presence of *Endamoeba histolytica*. This is by no means solely a tropical disease, as a considerable percentage of all individuals in the United States have been shown to harbor this organism. The fact remains that symptoms of *amebiasis* are more frequent and usually much more severe in tropical areas than they are in temperate zones. The chance of infection in the troops fighting in the most forward war zones is great because the necessity of hurried treatment of the drinking water may allow the cyst forms of the organism to pass through whatever process is used to render the water potable.

It is well known that different strains of *Endamoeba histolytica* vary greatly in their pathogenic capabilities. It is possible that there is a definite potential danger in the importation of new strains of this protozoal organism. This danger is heightened by the fact that the incubation period may be extremely long. Another danger is that the disease may become chronic and almost asymptomatic in undiagnosed or inadequately treated cases. Persons so affected can become a source of infection to their families and to larger groups with which they may come in contact. However, the medical profession has become much more cognizant of this type of dysentery since the Chicago epidemic of 1933 and the danger of *amebiasis* becoming much more widespread than it is at present is probably not particularly grave.

*Trypanosomiasis* possibly may be acquired by our troops stationed in two different areas. The African form of the disease, which is due to the presence of *Trypanosoma gambiense*, is found in equatorial Africa where many of our air transport lines have been placed. Men stationed there may acquire the infection without any clinical symptoms of disease until after return to the United States. Any spread of this form of the disease remains a relatively remote possibility, as the necessary vector, the tsetse fly, occurs only in Africa. Rigid vigilance in the spraying of airplanes and in quarantine inspection should prevent the establishment of the tsetse fly in the American tropics. Greatly encouraging results have followed the treatment of early cases of African trypanosomiasis by use of two new arsenical drugs, namely, melarsen oxide and a compound known as "70A." It appears therefore that we have little to fear from this disease.

American trypanosomiasis, due to *Trypanosoma cruzi*, might occur in personnel sent to Central or South America. This disease probably

will not become a serious problem because this particular form of trypanosomiasis usually is mild in adults. Cone-nosed bugs and some types of wild rodents in the southwestern United States harbor *Trypanosoma cruzi*, but as yet no naturally occurring cases in human beings have been reported.

*Leishmaniasis* is a chronic protozoal disease to which many of our troops undoubtedly are being exposed. It occurs in a visceral form, kala-azar, in the Mediterranean region, parts of India, northern China and in northeastern Brazil. The cutaneous form may be found in two main regions, one in North Africa and the Near East and the other in South and Central America. Scattered cases of leishmaniasis probably will occur in men returning from any of these parts of the world. The disease should not produce any serious postwar problems as the vector necessary for its propagation does not occur at the present time in our country.

*Schistosomiasis* is the only trematode infestation which is of sufficient potential danger to warrant discussion. Troops situated in areas where schistosomiasis is endemic may acquire this disease by immersion in water containing the infected snails. The larvae in the water are able to penetrate the skin even though the men so exposed are fully clothed. It is known that there is considerable specificity of the snails which are the intermediate hosts of these parasites. There is no definite proof that a species of snail exists in the United States which is capable of acting as an intermediate host in this particular disease. We do know that there are schistosomes of lower animals present in our country and the larvae of these forms are capable of producing a dermatitis in human beings, the so-called swimmers' itch. In view of this fact, there may be snails that are capable of acting as intermediate hosts in human schistosomiasis. If so, this infestation might possibly spread to the civilian population. This phase of the problem needs further study.

The possibility of importation of a few cases of *leprosy* is a problem which may assume undue importance in the minds of the civilian population because of the distorted ideas which most people entertain concerning the danger of this disease. A small number of cases of leprosy may develop among those men who have come into intimate contact with leprous natives. Clinical evidence of infection may not develop for years after their return to this country. We need not fear any wholesale spread of the disease because of these individual cases however, as experience with the Scandinavian cases brought to Minnesota years ago indicates that leprosy has a strong tendency to disappear spontaneously in most parts of the United States. Endemic foci of leprosy still remain in some regions of Texas, Louisiana and Florida, but the disease probably will not extend beyond these limits, except for occasional scattered cases of unexplained epidemiologic etiology.

*Coccidioidomycosis* is a fungous disease which, while not a tropical disease, is worthy of mention as a possible postwar problem. The



occurrence of this infection is confined practically entirely to the United States, and the endemic foci occur in California, Arizona and Texas. An especially large number of cases apparently originate in the San Joaquin Valley in California where several army camps have been located. Because the disease is apparently acquired by inhalation of dust containing spores, thousands of nonimmune individuals stationed in these areas for military maneuvers have been exposed to the infection. Thus, it is possible that there may be a great increase in the number of cases occurring throughout the country as these men are demobilized or discharged. Coccidioidomycosis gives rise to a symptom complex which may be difficult to diagnose at times, and hence the medical profession must be constantly aware of the possibility of encountering this disease. There is apparently no danger of the condition assuming widespread epidemic proportions as there is, evidently, no mechanism of direct transmission from person to person.

### CONCLUSIONS

1 Since the men and women of the armed forces of the United States are scattered over more widespread and far-flung areas of the earth than ever before in our history, they are being exposed to, and are being infected with, a greater variety of tropical diseases than ever before.

2 The importation of these diseases in our returning military personnel will present some postwar problems in medical practice, however, the dangers of widespread epidemics of these diseases extending into our civilian population have been for the most part greatly exaggerated.

3 The most important source of potential danger in the importation of these tropical diseases probably lies in the introduction of new and highly pathogenic strains of parasites which already exist in the United States, together with the importation of new insect vectors of diseases which have never before been present in our country.

4 The Army, Navy and United States Public Health Service are fully cognizant of these potential dangers and have organized new and rigid quarantine services to control as far as possible the importation of these diseases by military traffic.

5 The general medical profession is becoming better instructed in tropical diseases and the practice of good tropical medicine will be further bolstered by the return to private practice of thousands of young Army and Navy physicians who have had considerable training and experience in dealing with diseases of the tropics.

### REFERENCES

- 1 McCoy, O. R. Public health implications of tropical and imported diseases. *Am J Pub Health* 34 15-19 (Jan) 1944
- 2 Sawyer, W. A. Public health implications of tropical and imported diseases. *Am J Pub Health* 34 7-14 (Jan) 1944

## PENICILLIN METHODS OF ADMINISTRATION AND DOSAGE

WALLACE L. HERRELL

### LOCAL APPLICATION

CRUDE broth filtrates of cultures of *Penicillium notatum*, which contain penicillin, can be applied locally. This form of local treatment is of greatest value to those physicians who do not have available the more purified preparations of penicillin. These broth filtrates containing penicillin may be applied every few hours to infected lesions of the skin and soft tissue.

Either the sodium or the calcium salt of penicillin can be used for local treatment. The calcium salt is more satisfactory for this purpose than the sodium salt, particularly if the preparation is used dry and is applied to infected surfaces. The sodium salt in the dry state may cause local irritation and pain. Solutions of either the sodium or the calcium salt may be employed for local treatment of wounds that involve bone and soft tissue. They may also be used in the treatment of infections involving mucous membranes or certain body cavities (pleural space and joint cavities) as well as the eye. For this form of application physiologic saline solution or aqueous solution containing 500 to 1,000 Oxford units of penicillin per cubic centimeter is suitable. It is important to emphasize that solutions of penicillin are to be used for purposes of instillation and not for irrigation. If a solution of penicillin is used for irrigation the material does not stay in contact with the infected surface long enough to permit bacteriostatic activity.

For local treatment, penicillin may be applied in combination with sulfonamides or in the form of a cream. A suitable combination contains approximately 5,000 Oxford units of penicillin per gram of the sulfonamide. Sulfanilamide and sulfathiazole are the sulfonamides of choice for this purpose. It should be pointed out, however, that the local use of a penicillin-sulfathiazole preparation is not desirable in the treatment of infections involving the central nervous system. It is well known that sulfathiazole may produce irritation when it comes in direct contact with brain tissue.

When penicillin is incorporated into a cream for local use, it is recommended that the final preparation contain between 250 and 500 units of penicillin per gram. While penicillin may be used successfully in the local treatment of severe inflammatory lesions, the best results are more likely to be obtained when local therapy is combined with systemic penicillin therapy.

## INTRAMUSCULAR ADMINISTRATION

There are several methods available for the intramuscular administration of penicillin. The substance may be administered in saline solutions every three hours or it may be administered at longer intervals if penicillin is incorporated into some substance that tends to delay its absorption and therefore prolong its action. Penicillin may also be administered by the continuous intramuscular method.

When penicillin is administered intermittently in physiologic saline solutions, 10,000 to 20,000 Oxford units are dissolved in 2 c c of the sodium chloride solution. The injections are made every three hours, day and night. It is important to keep the size of the inoculum small in order to reduce the local discomfort attending the injection. A standard 22 gage intramuscular needle  $2\frac{1}{2}$  inches (about 6 cm) long is the most desirable for making these injections. Larger needles tend to increase the pain incident to the injection. Local irritation, however, may occur following these injections but serious difficulties are not, as a rule, encountered. One disadvantage of this method lies in the fact that at least eight injections are required in every twenty-four hours. Furthermore, the concentration of penicillin in the blood rises rather sharply during the first hour following intramuscular administration and then falls to a low value during the hour before the next injection is made. Sharp rises and falls in the concentration of an antibacterial agent in the blood are not, as a rule, desirable in the treatment of bacterial infections. This is particularly true in the presence of severe infections.

Morgan and his colleagues described a continuous intramuscular drip method for administration of penicillin. As much as 100,000 Oxford units of penicillin may be administered every twenty-four hours by this method. The entire amount to be used for the twenty-four hour period may be dissolved in a liter of physiologic saline solution and the rate of flow adjusted to permit the administration of this amount in twenty-four hours. According to Morgan and his colleagues, this method maintains a constant level of penicillin in the blood. Furthermore the administration can be accomplished with comparative freedom from pain on the part of the patient. The disadvantages of this method include the danger of local infection and abscess as well as the possibility that the total intake of fluid may thereby be restricted.

McAdam and his colleagues also have reported on this same method of administration. These investigators used 100,000 Oxford units per day in 100 c c of solution. When this method is employed, the rate of administration is regulated so as to deliver 100 c c in twenty-four hours (approximately 4 c c per hour). Under certain conditions this method of administration may be found very satisfactory.

An important contribution in connection with the intramuscular administration of penicillin is to be found in the report by Romansky

and Rittman. These investigators examined the possible use of beeswax and peanut oil as a vehicle for prolonging the action of penicillin. Mixtures containing as much as 6 per cent beeswax in peanut oil were used. To these mixtures were added varying amounts of penicillin. It has been found that following intramuscular injection of this material, made to contain as much as 100,000 Oxford units per cubic centimeter, adequate concentrations of penicillin can be maintained in the blood for twelve hours or longer. Penicillin may be present in the urine for twenty to thirty-two hours following this method of administration. This is an exceedingly important addition to the methods of administering penicillin. In the treatment of certain conditions wherein long periods of administration of penicillin are not necessary (gonorrhea, pneumonia and so forth), it may be possible to administer a complete course of treatment by means of a single intramuscular injection of the beeswax-peanut oil preparation. This method also may prove of value in the treatment of certain chronic infections wherein delayed absorption and prolonged action are desired.

The nonhygroscopic calcium salt of penicillin is the preparation of choice for addition to these mixtures of beeswax and oil. Such preparations, in addition to prolonging the action of penicillin, are fairly stable and may be kept at room temperature for a considerable period without giving evidence of loss of potency. If available, sesame oil is as good as, if not better than, peanut oil in the preparation of these mixtures containing beeswax and penicillin. Beeswax should not be mixed with animal oils as a vehicle for penicillin. If animal oils are employed, oil tumors are likely to develop after multiple injections. While beeswax-oil preparations are of value in the treatment of certain conditions, it is exceedingly important to use other methods in the treatment of overwhelming infections wherein immediate high concentrations of penicillin in the blood are desirable and are attainable immediately by intramuscular or intravenous administration.

Other studies on efforts to prolong the action of penicillin following its intramuscular administration have been reported by Trumper and Hutter. The principle that they employed is that chilling slows circulation in and around the site of an intramuscular injection. Therefore, one or two hours before a single, large dose of penicillin in physiologic saline solution was to be administered intramuscularly, an ice bag was applied at the site of injection and it was left in place for five to twelve hours after the injection. By use of this method, effective concentrations in the blood were maintained for at least five hours, as compared with two and a half hours when single doses were administered without chilling. The investigators obtained satisfactory results in treatment of patients suffering with gonorrhea when using single injections of 50,000 units of penicillin. They concluded that, if chilling was employed, bacteriostatic concentrations of penicillin could be maintained by giving two or three, instead of eight

to twelve, intramuscular injections over a period of twenty-four hours

Trumper and Hutter also pointed out that application of the ice bag in advance of injections of penicillin rendered the administration painless. In my experience, the application of an ice bag one-half to one hour before intramuscular injections are made is an exceedingly effective method for reducing the amount of pain at the site of local injection.

When intramuscular injections are to be made, it is also important that the injection be made by means of a sudden thrust of the needle into the tissues. Furthermore, it is important that the site of injection be changed frequently. The view is commonly held that penicillin should be administered only into the buttocks. However, it may be administered also into the deltoid muscles, thereby increasing the number of sites of injection.

#### INTRAVENOUS ADMINISTRATION

Penicillin may be administered intravenously by means of repeated single injections or by means of the continuous intravenous drip method. When penicillin is administered by the former method, it disappears from the blood stream even faster than after a single intramuscular injection. Furthermore, if penicillin is administered by single intravenous injection every three hours, eight separate venipunctures must be made each day. While this method has been used with satisfactory results, it is not the method of choice for intravenous penicillin therapy.

The continuous intravenous drip method best maintains a constant level of penicillin in the blood. It is the method of choice in the treatment of severe overwhelming infections such as bacteriemia. The technic is as follows: Half of the twenty-four hour dose of penicillin is dissolved in 1 liter of isotonic solution of sodium chloride. If the use of sodium chloride is undesirable, the material can be dissolved in a 5 per cent solution of dextrose made up in distilled water. However, the continuous administration of dextrose may of itself at times produce venous irritation. At the Clinic, therefore, we dissolve the material in dextrose only in those cases in which the use of sodium chloride is undesirable. Next, an 18 gage Lewisohn transfusion needle is inserted deeply into the vein, usually a vein of the arm, and is anchored with adhesive plaster. Use of veins on the dorsal surface of the hand or on the lateral aspect of the forearm allows the hand to be kept in pronation and renders this method of administration much less uncomfortable than when the material is administered with the arm in supination. A simple arm splint or bandage is applied to keep the arm in position. This method is tolerated well by the patient and renders the administration of penicillin fairly comfortable. It avoids eight separate intramuscular or intravenous injections in twenty-four hours. Some patients who receive penicillin in this fashion may sit up

at times during the course of the injection. It has been possible to administer penicillin without changing the needle or disturbing the apparatus in some instances for as long as eight days. Veins in the feet or legs can be used for this method of administration but the veins of the arm are preferred because complications following occasional venous irritation or thrombosis are considerably less severe if the veins affected are in the upper rather than in the lower extremity.

From what has just been written, it is evident that local venous irritation at the site of injection may attend the use of the continuous intravenous drip method. Parenthetically, it may be said here that such irritation seems especially likely to occur with certain batches of penicillin which may contain impurities. Careful inspection of the intravenous apparatus and changing the site of injection at the first sign of irritation usually are sufficient to cope with this difficulty. Although my colleagues and I have administered penicillin for as long as eight days through the same vein and into the same site of injection, it is often necessary to change the apparatus every few days. In my experience, venous irritation does not occur in more than 5 to 10 per cent of cases. In this connection should be mentioned the possible inclusion of heparin in intravenous infusions as a means of preventing thrombosis or venous irritation, which may occur when the intravenous drip method is used. This use of heparin was suggested by Marun, who found that 3 units of heparin per cubic centimeter of solution of penicillin made it possible to give the required amounts of penicillin without incident. He further pointed out that when infusions are given at the rate of 35 drops per minute, it would not seem possible to administer enough heparin to affect clotting time materially.

Now, to return to the technic of administration. Initially, 100 c.c. of the material is allowed to run into the vein at a fairly rapid rate. Following this the rate of injection is regulated to 20 to 30 drops a minute. The second liter is attached to the continuous intravenous system eight to ten hours later or whenever the material in the original bottle has been used. Repeated venipuncture is avoided by allowing saline or dextrose solutions to drip in slowly if, for any reason, administration of penicillin is unintentionally interrupted.

I have used as a rule, no more than 100,000 Oxford units per day and, in many instances, 40,000 units per day for intravenous therapy. Obviously, when increased supplies of penicillin are available, the problem of dosage may become of less and less significance. In our early work with penicillin low doses were employed in order to spread a small supply of penicillin as far as possible. If subsequent experience indicates that the hazard of delayed recurrence of the condition being treated is increased by using low dosage, obviously the amounts used must be increased. I consider, however, that 100,000 units per day is probably the maximal amount of penicillin necessary for treatment of those infections most commonly encountered. Delayed recurrences

in the presence of metastatic lesions may occur at times regardless of the amount of penicillin used

As I have already mentioned, the continuous intravenous drip method is the one of choice in the treatment of severe, overwhelming infections such as bacteriemia. Penicillin should be given by this route at least for the first few days of treatment. Under certain circumstances, the intermittent intramuscular method is entirely satisfactory. On the other hand, it is my impression that nearly twice as much penicillin is required for satisfactory intramuscular treatment as is required when the intravenous drip method is employed. That this is the case seems evident also from the report by White and others. They declared that in their opinion 100,000 units of penicillin, given by the intravenous drip method, are as effective as 200,000 units administered by the intramuscular method.

#### SUBCUTANEOUS ADMINISTRATION

Penicillin can be administered intermittently or continuously by the subcutaneous route. However, absorption of material administered subcutaneously is erratic. Moreover, concentrated solutions of penicillin may at times prove irritating when given subcutaneously. It appears, therefore, that the intravenous or intramuscular method of administration is preferable to the subcutaneous method.

#### INTRATHORACIC ADMINISTRATION

In the treatment of suppurative intrathoracic disease such as empyema, it often is desirable to supplement systemic therapy with instillations of penicillin into the pleural space. In some instances, empyema can thus be satisfactorily treated without resorting to surgical drainage. For intrathoracic treatment, 40,000 to 50,000 units of penicillin are administered daily. The amount to be used should be dissolved in 40 to 50 c.c. of physiologic saline solution and instilled directly into the pleural space following thoracentesis. It is recommended that this procedure be carried out once every twenty-four to forty-eight hours.

#### INTRA-ARTICULAR ADMINISTRATION

My colleagues and I<sup>5</sup> have reported studies which indicate that following systemic administration of penicillin antibacterial amounts of the material reach the fluid of inflamed joints. This is also true of the fluid of joints which are not inflamed. The amount of penicillin present in the joint fluid usually will be approximately half that found in the blood. Antibacterial amounts of penicillin may reach the joint fluid following intramuscular or intravenous administration. It is often desirable, however, to supplement systemic therapy by means of instillation of penicillin into the affected joints. This can be accomplished without any serious effects. Ten thousand to 20,000 Oxford units of

penicillin dissolved in 10 c.c. of isotonic saline solution can be instilled into infected joints after aspiration has been performed. Since penicillin remains in the structure for at least twenty-four hours, it is not necessary to repeat the injection oftener. The material can be administered every day or every other day for several times.

#### INTRATHECAL ADMINISTRATION

It is generally agreed by most investigators that penicillin does not readily diffuse into the cerebrospinal structures following its systemic administration. This appears certainly true of subjects suffering with certain diseases, such as syphilis, involving the cerebrospinal structures. It seems true, also, of the patient who, after being subjected on therapeutic indications to administration of penicillin and spinal puncture, yet is found to be normal. Although small amounts of penicillin may reach the cerebrospinal fluid in certain types of infections (acute meningitis for instance) it seems essential to supplement systemic therapy by daily instillations of 10,000 to 20,000 Oxford units of penicillin directly into the spinal canal. At least this should be done during the early period of treatment of severe diseases involving the spinal cord and meninges. This procedure, as a matter of fact, can be carried out for a considerable period without producing any important reactions. The amount of penicillin administered should be dissolved in 10 c.c. of isotonic solution of sodium chloride. Either the sodium or the calcium salt of penicillin has proved satisfactory for this form of treatment.

Five thousand to 10,000 units of penicillin can be instilled also once or twice daily into the ventricular system of the brain if small tubes have been left in place for this purpose at the time some surgical procedure is carried out.

#### INFUSION OF PENICILLIN BY WAY OF THE BONE MARROW

A satisfactory method for administration of various therapeutic agents by way of the bone marrow has been described by Tocantins and O'Neill. The sternum or clavicle can be used and, in children, the tibia or femur has been employed. It has been found possible to administer as much as 1 liter of solution by this route when the infusion needle was left in place for as long as sixteen hours. The average rate of infusion recommended by Tocantins and O'Neill was between 0.4 and 9 c.c. per minute. Likewise, Turkel and Bethell also have described a satisfactory instrument and technic for administration of fluids through the bone marrow.

Since either glucose or salt solution can be administered by way of the bone marrow, Morgan and his colleagues used this method for administration of penicillin in these solutions. It appeared from the report of Morgan and his colleagues, that as much as 46,000 units of penicillin could be administered in nine hours by this route. This



method, however, is not recommended except under very unusual circumstances, for instance, when suitable veins are not available or when, for any reason, as in the presence of extensive burns, the intramuscular or intravenous method is not considered practicable

#### PENICILLIN SNUFF

Snuff containing 5 parts of penicillin by weight, 5 parts of menthol and 90 parts of lycopodium has been recommended by some investigators<sup>3</sup> The material is administered by this route as often as every four hours Except in the most superficial types of infections in the nose, however, this method is not likely to be followed by satisfactory results unless, perhaps, systemic therapy also is employed

#### PENICILLIN AS AN INHALANT

It is evident from the report of Bryson and his colleagues that penicillin can be used as an inhalant It is so employed by having the patient breathe nebulized penicillin according to the standard procedure recommended for this purpose When this form of treatment is used (bronchitis and bronchiectasis), patients may inhale varying amounts of penicillin at regular intervals throughout the day One cubic centimeter of physiologic saline solution, containing 2,500 Oxford units of penicillin, can be nebulized and inhaled by a patient over a period of ten minutes This procedure can be carried out as often as three times an hour throughout the day, excluding time out for eating and sleeping As much as 75,000 to 80,000 Oxford units can be administered by this method This procedure must not be confused with vaporization methods, wherein the heat that is employed is likely to inactivate penicillin

#### ORAL AND INTRACOLONIC ADMINISTRATION

At present, the oral administration of penicillin is not entirely satisfactory and is not generally recommended The hydrochloric acid in the stomach will destroy most of the penicillin that is administered orally On the other hand, it was evident from the report of Free and others that at least some penicillin reaches the general circulation and is excreted in the urine following the oral administration of large doses (100,000 Oxford units) of penicillin to human subjects who had fasted for three to six hours before the penicillin was administered Enteric coating to protect penicillin against gastric acidity does not satisfactorily solve the problem since, when enteric coating is employed, penicillin may find its way into the large intestine, where it is inactivated by certain bacterial enzymes present there If a patient presents complete achlorhydria, penicillin can be administered by mouth and absorbed into the general circulation in amounts sufficient to justify this method of administration This method may be of value in the treatment of patients who have achlorhydria, therefore, if other acceptable methods are not practicable Whether pen-

icillin can be administered successfully by the oral route<sup>2, 6, 7, 9</sup> to human beings, alone, combined with antacids or in various vehicles, will depend on further trials

The intracolonic administration of penicillin is of no value for reasons which I have already mentioned.

## REFERENCES

- 1 Bryson, Vernon Sansome, Eva and Laskin, Sidney Aerosolization of penicillin solutions. *Science*. n.s. 100 33-35 (July 14) 1944
- 2 Charney Jesse, Alburn, H E. and Bernhart, F W Urinary excretion of penicillin in man after oral administration with gastric antacids *Science* n.s. 101 251-253 (Mar 9) 1945
- 3 Delaheld, M L., Straker Edith and Topley W W C. Antiseptic snuffs. *Brit. M. J.* 1 145-150 (Feb 1) 1941
- 4 Free, A H., Leonards J R., McCullagh D R. and Biro Barbara E. The urinary excretion of penicillin after oral administration to normal human subjects. *Science* n.s. 100 431-432 (Nov 10) 1944
- 5 Herrell W E., Nichols, D R. and Heilman, Dorothy H. Penicillin its usefulness limitations, diffusion and detection, with analysis of 150 cases in which it was employed. *J.A.M.A.* 125 1003-1010 (Aug 12) 1944
- 6 Libby R. L. Oral administration of penicillin in oil *Science*. n.s. 101 178-180 (Feb 16) 1945
- 7 Little, C. J H and Lumb George Penicillin by mouth *Lancet* 1 203-206 (Feb 17) 1945
- 8 McAdam, I W J., Duguid, J P and Challinor S W Systemic administration of penicillin *Lancet*, 2 336-338 (Sept. 9) 1944
- 9 McDermott, Walsh Bunn, P A., Benoit, Maria, DuBois Rebeckah and Haynes, Willetta Oral penicillin *Science*. n.s. 101 228-229 (Mar 2) 1945
- 10 Martin, Peter Heparin in intravenous infusions including penicillin therapy *Brit. M. J.* 2 308 (Sept 2) 1944
- 11 Morgan, H V., Christie, R V and Roxburgh I A Experiences in the systemic administration of penicillin *Brit. M. J.* 1 515-516 (Apr 15) 1944
- 12 Romansky M J and Ruttman G E. A method of prolonging the action of penicillin *Science*. n.s. 100 196-198 (Sept. 1) 1944
- 13 Tocantins, L M and O'Neill J F Infusion of blood and other fluids into the circulation via the bone marrow *Proc Soc. Exper Biol & Med* 45 787-783 (Dec.) 1940
- 14 Trumper Max and Hutter A M Prolonging effective penicillin action. *Science* n.s. 100 432-434 (Nov 10) 1944
- 15 Turkel, Henry and Bethell, F H A new and simple instrument for administration of fluids through bone marrow *War Med* 5 222-225 (Apr) 1944
- 16 White, W L., Flippin, H. F., Lockwood, J S and Murphy F D The indications for penicillin its dosage and administration. *Clinics* 3 309-323 (Aug) 1944

## OBSERVATIONS ON CHEMOTHERAPY OF CLINICAL AND EXPERIMENTAL TUBERCULOSIS

H CORWIN HINSHAW and WILLIAM H FELDMAN

THE need for an effective chemotherapeutic agent in treatment of clinical tuberculosis has led to extensive research, especially since the time of Ehrlich. While many compounds, especially gold salts, have been recommended and have found temporary clinical favor, the evidence for true therapeutic effect has not been convincing in any instance. The evidence submitted was subject to the unavoidable inaccuracies of clinical observation on a disease that has widely divergent clinical trends and so frequently tends to heal spontaneously in human beings. Prior to 1940 none of the alleged chemotherapeutic aids had demonstrated an ability actually to arrest the progress of tuberculosis experimentally induced in guinea pigs. The first compound that evinced the ability actually to arrest the progress of experimentally induced tuberculosis in guinea pigs was sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate (promin).<sup>6</sup>

The value of animal experimentation in the guidance of clinical research in treatment of infectious disease has been clearly demonstrated in recent years. Most, if not all, of the presently favored chemotherapeutic agents, which have proved to be so effective in treatment of many acute infectious diseases, have been discovered through methods of animal experimentation. A very close correlation has been shown to exist between the effect of most chemotherapeutic drugs on experimental infection induced in animals and the corresponding clinical disease naturally occurring in man. The correlation is not nearly so close between in vitro test tube methods and human disease. Because of this well-established value of animal experimentation in such problems, we believe that experimental tuberculosis of guinea pigs must continue to be the proving ground for any drugs that may be proposed for human administration.

The task of testing prospective chemotherapeutic drugs on experimental tuberculosis is infinitely more difficult than in the case of many acute diseases. Streptococcal and pneumococcal infections, for example, may be studied in a small animal such as the mouse and the disease produced may develop in such brief time that a great deal of information may be obtained within a few days with a very small amount of drug. In the case of tuberculosis the disease requires weeks or months to develop and the smallest practicable animal is the guinea pig, requiring an expenditure of time and drug much greater than is required in the case of streptococcal or pneumococcal infection. It appears probable, therefore, that a period of years will be required

to achieve full understanding of the therapeutic potentialities of any large number of compounds. During the past five years only a few score of compounds have received adequate study in experimental animals and of these only four have reached the stage of extensive study on clinical tuberculosis, promin, diasone, promizole and streptomycin.

#### PROMIN (SODIUM P P-DIAMINODIPHENYLSULFONE-N N'-DIDEXTROSE SULFONATE)

It has been clearly shown<sup>7</sup> and repeatedly confirmed<sup>1, 8, 10</sup> that promin has the power of inhibiting the development of lethal tuberculosis in the experimentally infected guinea pig. The duration of life of treated animals may be extended, perhaps indefinitely, so long as treatment is continued. During this period the animals appear to remain in perfect health. Treatment has been continued for as long as one year, long after all untreated control animals have succumbed. At necropsy, treated animals frequently have no recognizable lesions of tuberculosis when observed grossly or there may be residual indolent lesions in the regional lymph nodes adjacent to the sites of subcutaneous inoculation, in the tracheobronchial lymph nodes and rarely in the viscera. Microscopic examination, however, will frequently reveal the presence of small stabilized or healing lesions, which would not have been observed had sections not been made. In such residual lesions the histologic picture may be that resembling the various steps of healing, including resolution, fibrosis, encapsulation and even calcification. Caseation necrosis is rarely seen and the tubercles observed are commonly of the so-called hard or epithelioid type. This is in striking contrast to the much more extensive and obviously progressive destructive lesions uniformly seen in all untreated control animals. It is important to emphasize that animals that have been treated even for prolonged periods with promin and appear to possess only lesions of healing type or even those that have no demonstrable lesions, still harbor virulent tubercle bacilli, which can be recovered when emulsions of spleen are used for the inoculation of other guinea pigs or even by cultural methods for isolation of tubercle bacilli.

Efforts to utilize promin in treatment of clinical tuberculosis have been under way during the past four years.<sup>3, 8</sup> It was soon revealed that human beings do not tolerate promin in doses comparable to those that produce the therapeutic effect in experimental guinea pigs. In deed, more than a half of all patients are unable to take even small doses of promin, either because of uncomfortable reactions or because of the development of mild to moderate anemia when treatment is extended over many weeks or months. The poorest drug tolerance is demonstrated by those failing patients who are most in need of some chemotherapeutic aid. Experience has suggested to us that patients in terminal phases of pulmonary tuberculosis tolerate promin so poorly that the drug is definitely contraindicated because it contributes to

the discomfort of such patients and in no instance has it appeared to reverse the downward trend of desperately ill patients. In such instances the pathologic character of the disease in human beings is quite different from that of recently infected tuberculous guinea pigs. More suggestive effects have been noted in recent lesions of pulmonary tuberculosis, especially those known to have existed for only a few weeks and among patients whose general condition is reasonably good. We have had the opportunity of observing only a moderate number of such patients, those who have tolerated promin in adequate dose to yield a blood level in excess of 2 or 3 mg per 100 c c have shown encouraging progress. It is exceedingly important to indicate, however, that in all instances the lesions of these patients have been such as tend to resolve spontaneously and sometimes very rapidly under the influence of rest in bed alone. Because of this we have not felt justified in drawing any conclusion as to the therapeutic efficacy of promin in cases of pulmonary tuberculosis.

Promin has been administered by the oral route to all the experimentally infected guinea pigs in our studies and also we have chosen to administer it by the oral route over prolonged periods to those patients who have received this drug. It is also possible to administer promin parenterally and, when the drug is so given, the uncomfortable and potentially hazardous toxic results are rarely noted. Zucker, Pinner and Hyman<sup>12</sup> have attempted to treat clinical tuberculosis by administering promin in large doses over brief periods by the intravenous route but their results were wholly disappointing. It seems probable to us that orally administered promin is modified, perhaps by hydrolysis, to produce some compound resembling diaminodiphenylsulfone but that when administered intravenously the drug is excreted too rapidly to undergo similar change.

Somewhat more encouraging results have been noted in a small number of patients who had extrapulmonary tuberculosis, especially osseous lesions with draining sinuses.<sup>11</sup> Here, again, the small number of cases and the lack of an adequate control series have made it impossible to draw definite conclusions. It has also appeared doubtful to us if closely controlled clinical studies should be carried out with a drug such as promin, which is so difficult to administer over prolonged periods by the oral route. We have directed our efforts toward the study of less toxic compounds in recent months.

A few patients who had tracheobronchial tuberculosis of ulcerating type have received promin, either by repeated supraglottic intratracheal administration or, more recently, by inhalation of nebulized promin solution.<sup>2 3 4 11 12</sup> It has been noted that promin is well tolerated when administered in this manner and sufficient improvement has been noted to suggest the possibility that more extensive study of this approach to treatment of these difficult lesions could be carried out. This will be possible in the near future when the promin solution is made available commercially.

Promin may also be applied topically to superficial lesions of tuberculosis such as draining sinuses in the thoracic wall, sinuses from tuberculous lymphadenitis and possibly some types of cutaneous tuberculosis. The most convenient method of applying promin to these lesions is in the form of a jelly, similar to that which has been under trial in England.<sup>11</sup> Results have been sufficiently suggestive to lead to the early appearance of this preparation, also, on the market. Promin jelly applied topically rarely produces any toxic manifestation whatever. It is anticipated that this will receive wide study within the next year or two, after which more definite conclusions may be reached.

#### DIASONE (DISODIUM FORMALDEHYDE SULFOXYLATE DIAMINODIPHENYL SULFONE)

Diasone is very similar to promin chemically, although lacking the glucose molecule present in promin and with a change of valence of the sulfur atoms that are attached to the end chains. It should be anticipated that diasone, like promin, should undergo hydrolysis in the human body to some compound resembling diaminodiphenylsulfone. Diasone has been studied in experimental tuberculosis of guinea pigs and possesses very similar properties to those described for promin in previous paragraphs. We have had no direct personal experience in the administration of diasone to patients who had clinical tuberculosis and results that have been reported are conflicting. Several groups are now investigating diasone clinically and it is anticipated that more information will be available before many months. It appears wise to withhold judgment until some concerted opinions have been expressed.

Diasone was brought into general prominence by the appearance in lay publications of uncritical opinions, which were widely disseminated and, of course, eagerly seized on by many victims of tuberculosis, some of whom have been disillusioned. The most unfortunate result has been the tendency of such patients to refuse acceptance of known effective treatment for tuberculosis especially sanatorium care and collapse therapy.

#### PROMIZOLE (4,2-DIAMINOPHENYL-5-THIAZOLESULFONE)

Promizole is of unusual interest because of the fact that it possesses similar properties to those already described for promin and diasone in effectively controlling the development of experimental tuberculosis in guinea pigs and especially because of the fact that its chemical structure is basically different, having a heterocyclic nucleus to the molecule, which could readily be the beginning of a new series of compounds. This interest was greatly heightened by the observation that patients were able to tolerate promizole in doses quite comparable to those administered to guinea pigs and that blood concentrations of comparable degree were noted in such patients.

Observations on promizole in cases of clinical tuberculosis have been under way during the past two years in collaboration with several other clinicians but results have not yet been published. It may be stated at this time, however, that as yet no fully convincing evidence of striking therapeutic effect has been observed in our experience.

### STREPTOMYCIN

It has been shown recently<sup>5</sup> that streptomycin is effective in treatment of experimental tuberculosis of guinea pigs. We and our associates have utilized streptomycin in treatment of twenty-two patients with clinical tuberculosis since December, 1944 and have not noted serious toxic effects, even after prolonged administration of large doses. Any decision as to its therapeutic efficiency must await more extensive study.

### REFERENCES

- 1 Armstrong, A. R., Rae, M. V., Lucas, C. C. and Greey, P. H. Effect of promin on experimental tuberculosis. *Am Rev Tuberc* 50 160-162 (Aug) 1944
- 2 Barach, A. L. Principles and practices of inhalational therapy. Philadelphia, J. B. Lippincott Company, 1944, 315 pp.
- 3 Dancey, R. J., Schmidt, R. H., Jr. and Wilkie, J. M. Promin in pulmonary tuberculosis, a progress report. *Am Rev Tuberc* 49 510-534 (June) 1944
- 4 Edlin, J. S., Bobrowitz, I. D., Safford, F. L., Jr. and Butler, F. S. Promin inhalation therapy in pulmonary tuberculosis. *Am Rev Tuberc* 50 543-555 (Dec.) 1944
- 5 Feldman, W. H. and Hinshaw, H. C. Effects of streptomycin on experimental tuberculosis in guinea pigs: a preliminary report. *Proc Staff Meet, Mayo Clin* 19 593-599 (Dec 27) 1944
- 6 Feldman, W. H., Hinshaw, H. C. and Moses, H. E. The effect of promin (sodium salt of p,p'-diamino-diphenyl-sulfone-N,N'-dextrose sulfonate) on experimental tuberculosis: a preliminary report. *Proc Staff Meet, Mayo Clin* 15 695-699 (Oct 30) 1940
- 7 Feldman, W. H., Hinshaw, H. C. and Moses, H. E. Promin in experimental tuberculosis, sodium p,p'-diaminophenylsulfone-N,N'-didextrose sulfonate. *Am Rev Tuberc* 45 303-333 (Mar) 1942
- 8 Hinshaw, H. C., Pfuetze, K. H. and Feldman, W. H. Chemotherapy of clinical tuberculosis with promin, p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate, a second report of progress. *Am Rev Tuberc* 50 52-57 (July) 1944
- 9 Medlar, E. M. and Sasano, K. T. Promin in experimental tuberculosis in the guinea pig. *Am Rev Tuberc* 47 618-624 (June) 1943
- 10 Steenken, W., Jr., Heise, F. H. and Wolinsky, E. Treatment of experimental tuberculosis in the vaccinated and nonvaccinated guinea pig with promin. *Am Rev Tuberc* 48 453-460 (Dec) 1943
- 11 Tyder, W. H. and Lapp, A. D. Treatment of superficial tuberculous lesions by local application of promin. *Brit M J* 2 748-749 (Dec 26) 1942
- 12 Zucker, Gary, Pinner, Max and Hymn, H. T. Chemotherapy of tuberculosis, promin by the intravenous drip method. *Am Rev Tuberc* 46 277-284 (Sept.) 1942

# RHEUMATIC FEVER, A SUMMARY OF PRESENT DAY CONCEPTS

ARLIE R. BARNES

THE prevalence of rheumatic fever in the armed forces has emphasized again that it is a major medical problem. The decision had to be reached not to reject for military service those individuals who had had an attack of rheumatic fever provided evidence of heart disease was absent. Since an attack of rheumatic fever is evidence that the selectee is a "susceptible" and hence bears a greater than average liability of recurrence of rheumatic fever, such a plan is not ideal from a public health point of view. However, administrative problems involved in the rejection of such selectees appeared to make their exclusion impractical. The medical personnel of the armed services is confronted with the problem of diagnosis and prevention of rheumatic fever and of the disposal of those individuals who have an attack while in the service.

## EPIDEMIOLOGY

Rheumatic fever occurs most commonly in childhood and adolescence, the average time of the first attack being in the seventh or eighth year of life. A distinct familial incidence is conceded, in which respect the disease is like tuberculosis. Wilson,<sup>7</sup> and others have presented much evidence that heredity is a very important factor in predisposing to its occurrence. Much evidence is available that there are marked sectional and climatic differences in the incidence of rheumatic fever. The disease has a high incidence in the Rocky Mountain and New England states but fewer cases occur in the warmer southern portion of the United States. The disease has its lowest incidence in the summer months and its greatest prevalence in the cold and wet months of the year. Rheumatic fever is believed to be more common among the less favored economic groups in which the ill fed, the ill clothed and the ill housed are included. Wilson did not find this to be true and the British Medical Research Council<sup>8</sup> did not find this economic factor to be of prime importance in the occurrence of the disease.

Rheumatic fever should be regarded as an epidemic disease. There is a close association of initial and recurrent attacks of rheumatic fever and infections caused by hemolytic streptococci. If careful sampling of throat cultures of new recruits reveals a high incidence of infection due to hemolytic streptococci the prediction may be made that rheumatic fever will appear in the group in considerable incidence in from ten days to three weeks (Massell and Jones<sup>4</sup>). A considerable number of patients known to be susceptible to rheumatic fever and exposed to such an epidemic likewise will have a recurrence of the disease.



## ETIOLOGY

At the present time the cause of rheumatic fever is unknown. Much evidence suggests a causal relation with hemolytic streptococci. Also, there is much to indicate that allergic reactions play an important role in its production. Investigators postulate an individual in a state of hypervulnerability or allergic irritability (Swift, Derick and Hitchcock<sup>6</sup>) or they conceive that the disease results from an allergic response of tissues which have been sensitized previously by a specific or nonspecific streptococcic infection.<sup>7</sup> The occurrence of group A beta-hemolytic streptococci in respiratory infections, which frequently precede rheumatic fever, is well established according to Massell and Jones but the specific relation of these organisms to rheumatic fever awaits experimental reproduction of the disease.

## DIAGNOSIS

The diagnosis of rheumatic fever presents real difficulty at times. One has to guard against the error of dismissing minor evidences of the disease with consequent failure to recognize the disease on the one hand, and, on the other, the error of concluding that rheumatic fever exists on the basis of inadequate clinical grounds with all the unfortunate consequences which such a mistaken diagnosis entails. The diagnosis of rheumatic fever probably rests on a sound basis if several of the following manifestations are present in a case (Jones<sup>2</sup>):

- 1 Carditis. Evidence of carditis is definite cardiac enlargement, significant cardiac murmurs, pericarditis or congestive heart failure. Electrocardiographic changes which include prolongation of the auriculo-ventricular conduction time, inversion of the T waves and the peculiar elevation of the S-T junction (pericarditis) are important evidence of myocardial injury and constitute corroborative evidence of carditis.
- 2 Arthralgia. Tender, red, swollen joints, particularly if there is a migratory character to their involvement, are strongly suggestive of rheumatic fever. However, as Jones remarked, in cases in which this manifestation constitutes the only symptom one must remain skeptical.
- 3 Chorea. Since chorea develops in half of the cases of rheumatic fever in which the patients are young persons and since definite evidence of rheumatic fever (Jones) eventually develops in three-fourths of the cases of chorea, this symptom is very important, when present, in corroborating the diagnosis.
- 4 Recurrence of rheumatic fever. The presence of mild symptoms of rheumatic fever occurring in an individual with a definite history of the disease or signs of rheumatic heart disease are very significant evidence for a positive diagnosis.

Not every patient who has rheumatic fever has the combined symptoms of respiratory infection with sore throat, migratory swelling and redness of the joints, chorea and fever. There are many cases in which respiratory infection and sore throat are followed only by vague

articular pains with perhaps only one or two joints involved and with little redness or swelling of a very transitory nature. This articular involvement may be so slight as to be overlooked by the patient and physician unless a high index of suspicion of rheumatic fever is entertained. A low-grade fever, which may not exceed  $100^{\circ}\text{F.}$ , may persist longer than would be expected with the usual infection of the upper part of the respiratory tract. In such cases rheumatic fever must be suspected and the patients must be kept under observation for a considerable time. This is especially important if the patient is one of a group in which an epidemic infection with beta hemolytic streptococci or an epidemic of scarlet fever is known to exist or if the patient is one of a group in which an epidemic of rheumatic fever is prevalent. When such patients are kept under observation the sedimentation rate of the erythrocytes may remain elevated, electrocardiographic evidence of delayed auriculoventricular conduction may appear and evidence of cardiac involvement in the form of significant murmurs, pericarditis and cardiac enlargement eventually may appear. Unless more suspicion is attached to these innocent attacks in young adults, many instances of rheumatic fever will be overlooked and many patients will be deprived of a proper convalescent program which would afford them the maximal protection from serious cardiac damage.

It must be emphasized that an unwarranted diagnosis of rheumatic fever should not be made. The connotation of an unwarranted diagnosis is such that, although the diagnosis later is disproved, the patient is left with a cardiac neurosis that it is next to impossible to eradicate in many instances. Since other diseases, such as rheumatoid arthritis, tuberculosis, lupus erythematosus and undulant fever, to mention only a few, may give rise to symptoms simulating rheumatic fever, observation of the patients for months or years may be required to arrive at a true diagnosis (Jones).

#### TREATMENT

Rest still remains the essence of the treatment of rheumatic fever. Its optimal duration is scarcely the same in any two cases but certainly it must be continued until fever and involvement of the joints disappear, until the sedimentation rate is normal and until the electrocardiographic changes have disappeared. Persistent cardiac enlargement or any evidence of myocardial failure are indications for prolonged rest.

Salicylates administered by mouth in large doses reduce the fever and relieve pain but there is no evidence that they shorten the attack. Recently, Coburn<sup>1</sup> has advised the intravenous administration of large amounts of salicylates with a view to maintaining a high concentration of the drug in the blood stream. His preliminary observations arouse hopes that this method may be very effective, but further ex-

perience with this type of treatment will be required to determine and establish its efficacy

#### PREVENTION OF RHEUMATIC FEVER

The work of Jones<sup>8</sup> indicates the close relation that exists between certain outbreaks of respiratory infection in which hemolytic streptococci are concerned and the subsequent development of rheumatic fever in many of the individuals so infected. It is only by careful bacteriologic studies that the evidence of a high incidence of hemolytic streptococci in individuals with respiratory infection can be established. Once the presence of these organisms is established, segregation may be feasible. There is evidence that the spread of infection is particularly prone to occur during sleeping hours and especially when large numbers of people are sleeping in a single room. It is not known as yet whether the administration of sulfonamide drugs to groups of people known to harbor hemolytic streptococci in their respiratory passages will reduce the likelihood of contagion or prevent the occurrence of rheumatic fever subsequently in individuals so infected. However, this is an approach that is receiving careful study. Jones said that there is some evidence that the daily administration of salicylates, starting at the time of a respiratory infection with hemolytic streptococci, may in some way greatly decrease the probability that rheumatic fever will develop subsequently.

Just as susceptibility of individuals and families to rheumatic fever is an accepted fact, it also can be said that one who has had rheumatic fever is more liable to a subsequent attack. It appears, moreover, that such an individual runs his greatest hazard if he acquires a respiratory infection due to hemolytic streptococci. There are numerous reports, hard to evaluate, it is true, indicating that the daily administration of a sulfonamide drug to such an individual greatly limits such respiratory infections and hence reduces his chance of having a recurrent infection with rheumatic fever. To offset the possible advantages of such a program is the danger of developing drug sensitivity and drug fast strains so that its adoption on a large scale must await much more study of not only its effectiveness but of its possible dangers.

Some effort can be made to minimize the exposure of persons who have had rheumatic fever to respiratory infection and particularly to infections due to hemolytic streptococci. The studies of the British Medical Research Council and of Wilson indicate that recurrences are less common among persons who are well housed, well clothed and well fed. There is considerable evidence that recurrences are diminished if the patient can be moved to a warmer and possibly drier climate. This procedure has been utilized by the armed services but it is not as feasible for the civilian population for economic reasons. It is desirable that susceptible soldiers not be quartered with new recruits, among whom epidemics of respiratory infections are common in the

first few weeks after induction. Whenever possible, individual sleeping quarters or sleeping quarters with only one other person reduce the chances that a susceptible individual will acquire a respiratory infection.

#### INSTRUCTION OF PATIENTS WHO HAVE RECOVERED FROM RHEUMATIC FEVER

One of the gravest responsibilities that confronts a physician is the advice he gives a patient who has recovered from rheumatic fever. Physicians are seeing too many civilians, and particularly too many discharged soldiers, who have derived wittingly or unwittingly nothing but hopelessness from this advice. It is difficult to disabuse their mind of its anxieties, and without such corrective measures these individuals become confirmed cardiac neurotics and suffer far more from this neurosis than they ever will from their heart disease.

It is well to bear in mind that only a small percentage of patients who have had rheumatic fever become disabled by heart disease and succumb by mid-adult life. Since this observation applies to children and since the incidence of serious heart disease following rheumatic fever which occurs first in adult life appears to be less than it is in children, it is with these adults that one should be particularly careful that the matter is presented in a proper manner. If they recover with a heart that is normal in size, notwithstanding the fact that they may have a cardiac murmur, it should be pointed out to them that such a situation is usually compatible with a life of normal activity and usefulness provided they do not have one or more recurrent rheumatic infections. They should be warned that their special problem is the avoidance of and the meticulous care of, respiratory infections. Although physicians do not know as much about the prevention of such infections as can be hoped that the future will provide, the patients can be warned against conditions of exposure, unnecessary exposure in crowds during epidemics of respiratory infection, loss of sleep and all other unhygienic measures which are believed to lower resistance. If feasible, they may be advised that residence in the warmer or drier latitudes of the United States will afford some measure of protection. Above all, physicians have an obligation to orient the patient to his illness and its relation to his future life so that one more will not be added to the already overlarge population of neurotics.

#### SUMMARY

Rheumatic fever is a huge problem not only in civilian life but in the armed forces. It is a disease in which individual and familial susceptibility plays a large role. It is related to climatic conditions and is prevalent at that time of year when respiratory infections attain their greatest proportions. Although its cause is not known, there are many facts which suggest that it follows in the wake of respiratory infection due to hemolytic streptococci. The clue to the prevention of initial and recurrent attacks may lie in a more precise knowledge of

this relationship and in measures which may permit physicians to prevent rheumatic fever once they know that respiratory infections due to hemolytic streptococci are at hand. It is possible that the sulfonamide drugs, salicylates or other drugs yet unknown will be found either to limit the incidence of such respiratory infections or provide a cure for rheumatic fever itself. Certainly, more productive investigation of these possibilities is being stimulated by the problems presented in the armed services. Too much emphasis cannot be directed to the responsibilities physicians have to instruct all who have recovered satisfactorily from rheumatic fever in such a way that they do not become cardiac neurotics. Such an attitude in these patients is tragic and easily can be avoided if only a little time is taken with each patient to orient him in a proper outlook on his situation.

## REFERENCES

- 1 Coburn, A. F. Salicylate therapy in rheumatic fever, rational technique. *Bull Johns Hopkins Hosp* 73 435-464 (Dec ) 1943
- 2 Jones, T. D. The diagnosis of rheumatic fever. *J.A.M.A.* 126 481-484 (Oct. 21) 1944
- 3 Jones, T. D. Personal communication to the author
- 4 Massell, B. F. and Jones, T. D. Some practical aspects of the rheumatic fever problem which have an important bearing in military medicine. *Am Heart J* 27 575-587 (Apr ) 1944
- 5 Medical Research Council. Child life investigations, social conditions and acute rheumatism. Special Report Series, No. 114, London, 1927, 108 pp
- 6 Swift, H. F., Derick, C. L. and Hitchcock, C. H. Rheumatic fever as a manifestation of hypersensitiveness (allergy or hyperergy) to streptococci. *Tr A Am Physicians* 43 192-202, 1928
- 7 Wilson, May G. Rheumatic fever, studies of the epidemiology, manifestations, diagnosis, and treatment of the disease during the first three decades. New York, The Commonwealth Fund, 1940, 595 pp

# THE CLINICAL USE OF DICUMAROL

NELSON W BARKER

IN 1941 Link and his associates<sup>7 13</sup> reported the isolation and synthesis of dicumarol [3,3'-methylenebis (4 hydroxycoumarin)] Since that time a number of reports<sup>1 2, 5 6</sup> have been made on the physiologic effects of this drug on animals and human beings At the Clinic dicumarol has been administered to more than 1,000 surgical patients during the postoperative period for the purpose of preventing postoperative thrombosis and embolism and it has also been administered to more than 100 nonsurgical patients who had various types of arterial and venous thrombosis and embolism for the purpose of preventing or inhibiting the progress of their disease This report is based on the study of these patients

## QUESTIONS AND ANSWERS

What is the physiologic effect of dicumarol on human beings?—Dicumarol produces prothrombin deficiency as indicated by the Quick prothrombin time test<sup>5 6</sup> The prothrombin deficiency may be mild or severe depending on the amount of the drug given over a period and by the individual susceptibility of the patient to the drug As a secondary effect of prothrombin deficiency the coagulation time of the blood (Lee-White) may be, but is not necessarily, prolonged The degree of prolongation of the coagulation time does not necessarily parallel the degree of prolongation of the prothrombin time Thus the coagulation time cannot be used as an index of the effect of the drug on an individual patient Dicumarol usually prolongs the clot retraction time and elevates the sedimentation rate of the erythrocytes Some recent work<sup>12</sup> indicates that it may inhibit platelet adhesiveness. Otherwise the drug does not appear to have any physiologic or toxic effects on human beings Even after prothrombin deficiency of moderate to severe degree has been maintained for more than two months by administration of dicumarol, the ordinary tests of hepatic function have been found to give negative results and no untoward effects have been noted

Does dicumarol prevent thrombosis in human beings?—The evidence that the prothrombin deficiency produced by dicumarol prevents thrombosis in human beings has come largely from statistical studies of postoperative patients At the Clinic it was found that among 678 patients who had a pulmonary embolism and survived and who did not receive dicumarol 297 (43.8 per cent) had one or more subsequent episodes of thrombophlebitis or pulmonary embolism and 124 (18.3 per cent) had a subsequent fatal pulmonary embolism<sup>4</sup> Among 180 similar patients who had pulmonary embolism and survived and

did receive dicumarol, only two (1.1 per cent) had subsequent thrombophlebitis or embolism and only one (0.6 per cent) had a subsequent fatal embolism. Also among 897 patients who had postoperative thrombophlebitis (or phlebothrombosis) and who did not receive dicumarol, ninety-five (10.6 per cent) had one or more subsequent episodes or extensions of the thrombophlebitis and fifty-one (5.7 per cent) had subsequent fatal pulmonary embolism.<sup>4</sup> Among 138 similar patients who received dicumarol four (2.9 per cent) had more thrombophlebitis and none had fatal embolism.

Sixty-one patients who have had thrombophlebitis or embolism at some time prior to operation have been given dicumarol prophylactically and none have had thrombosis or embolism after operation. Dicumarol has been given prophylactically to 438 patients on whom abdominal hysterectomy had been performed and who had not had thrombophlebitis or pulmonary embolism. In a previous study it had been found that the risk of thrombophlebitis and embolism in these patients was 4 per cent and the risk of fatal embolism 0.7 per cent.<sup>3</sup> No embolisms developed in the 438 patients who received dicumarol. Two of these patients had minor thrombophlebitis of the veins of the calf but only after they had left the hospital and after the prothrombin had returned to normal. The nonsurgical patients who received dicumarol had various diseases characterized by thrombosis and included patients who had thrombophlebitis or pulmonary embolism, complicating infectious diseases, blood dyscrasias, congestive heart failure and severe injuries, recurrent idiopathic thrombophlebitis, intracardiac thrombosis with arterial embolism, simple arterial thrombosis, thrombo-angitis obliterans and arteriosclerosis obliterans. In none of these cases was there any evidence that thrombosis or embolism developed during the period in which the prothrombin time was elevated as the result of administration of dicumarol.

How important is the Quick prothrombin time test as a guide to the administration of dicumarol?—The purpose of administration of dicumarol is to produce a definite but not excessive prothrombin deficiency. If as a result of administration of dicumarol the prothrombin is less than 30 per cent of normal, thrombosis will almost certainly not develop and if the prothrombin is greater than 10 per cent of normal, bleeding will almost certainly not occur. Therefore in any individual case it is necessary to keep the prothrombin between 30 per cent and 10 per cent of normal to achieve the desired effect. Patients vary considerably in their sensitivity to the drug and this variability is usually unpredictable. Furthermore the effect of dicumarol is delayed, developing twenty-four to seventy-two hours after a dose is given, and it may persist for several days after reaching a maximum. For these reasons it is absolutely necessary to do daily prothrombin time tests<sup>10, 11</sup> (Quick method) on a patient who is receiving dicumarol in order to know each day whether or not the prothrombin is within

the desired limits and to determine when another dose of the drug should be given.

In doing the Quick prothrombin time test, thromboplastins of different potency, giving different normal prothrombin times and therefore different prothrombin times for certain degrees of prothrombin deficiency, are used in different hospitals and clinics. Also, unfortunately, thromboplastins may vary considerably in their potency even when prepared from similar sources and in the same way.<sup>9</sup> For any type of thromboplastin which is used and when any new batch of thromboplastin is prepared, prothrombin times should be determined for 10 per cent, 20 per cent and 30 per cent dilutions of normal plasma. The results will be essentially the same if the dilutions are made with either prothrombin-free plasma or physiologic solution of sodium chloride. It is important that the physician who is supervising dicumarol therapy know each day the values in terms of prothrombin time in seconds for these three dilutions of normal plasma which can be considered as values for 10 per cent, 20 per cent and 30 per cent of normal prothrombin respectively.

What is the dose of dicumarol?—Dicumarol is effective when administered orally. A satisfactory preparation for parenteral use has not been developed. The following plan of dosage has been found to be simple and satisfactory and is recommended. All the dicumarol for one day is given in a single dose after the prothrombin time has been determined for that day. Three hundred milligrams are given the first day and 200 mg are given on each subsequent day that the prothrombin is greater than 20 per cent of normal. No dicumarol is given on days when the prothrombin is less than 20 per cent of normal. For the occasional patient who is found to be resistant to the drug the subsequent doses may be increased to 300 mg and if the patient is very sensitive to the drug, as indicated by rapidly developing and persistent severe prothrombin deficiency (below 10 per cent) after the usual doses, the dose may be reduced to 100 mg.

If dicumarol is given after a surgical operation for prophylaxis against thrombosis, administration is begun on the third postoperative day. When dicumarol is given to surgical patients prothrombin deficiency should be maintained until the patient leaves the hospital and for at least four days after he has been ambulatory. Daily prothrombin time tests should be done until the administration of the drug is discontinued. When dicumarol is given to nonsurgical patients the desirable duration of the prothrombin deficiency may be quite variable. If adequate protection against thrombosis and embolism is desired, the prothrombin deficiency should be maintained until the patient is ambulatory and in some instances for a considerably longer time. However, close observation of the patient and daily prothrombin time tests should be continued for the entire period.

Is dicumarol a dangerous drug?—The only untoward effect which has



been observed in human beings after dicumarol has been administered has been bleeding. If the contraindications to administration of dicumarol are observed and if the drug is administered according to the plan mentioned in the previous section the danger of bleeding is minimal. Minor epistaxis and microscopic hematuria may occur during administration of dicumarol but they may be disregarded. More serious bleeding may occur from recent operative wounds or ulcerative lesions, particularly of the gastro-intestinal tract. Usually such bleeding is not primarily caused by the prothrombin deficiency but what might have been minor transient bleeding becomes prolonged bleeding because of the prothrombin deficiency. Multiple widespread ecchymoses and hemorrhages are extremely rare. Definite bleeding is rare if the prothrombin does not fall below 10 per cent of normal and only occurs in about 4 per cent of cases when the prothrombin does fall below 10 per cent of normal. Among the first 1,000 patients who received dicumarol during the immediate postoperative period the incidence of serious bleeding was 2.5 per cent. Among the 318 patients who had had thrombophlebitis or pulmonary embolism it was only 1 per cent. Only one fatality from hemorrhage occurred among the 1,000 patients who received dicumarol during the postoperative period and in this case it is doubtful that the dicumarol was a factor, since there was relatively little prothrombin deficiency when bleeding occurred. The experience at the Clinic has been that, when properly used, dicumarol is no more dangerous than many other potent drugs.

**How can excessive prothrombin deficiency or bleeding be controlled?**—In using the plan of dosage recommended in this paper, patients may be encountered who have excessive prothrombin deficiency (below 10 per cent of normal) after the first one or two doses of the drug. Such patients usually are among the group who have recent or prolonged dietary deficiency or lesions of the gastro-intestinal tract and are usually those who have not had previous thrombosis or embolism. This excessive prothrombin deficiency can be restored to within safe limits in about 90 per cent of cases by a single intravenous injection of a large dose (60 mg.) of menadione bisulfite (2-methyl-naphthoquinone monosodium bisulfite).<sup>8</sup> Thereafter dicumarol should be given more cautiously or in 100 mg. doses to that patient. If bleeding occurs during administration of dicumarol 60 mg. of menadione bisulfite should be given intravenously and the patient should be transfused with 500 c.c. of freshly drawn citrated blood, which will usually cause the bleeding to stop within a few hours. Rarely, subsequent transfusions and injections of menadione bisulfite may be necessary.

**What are the deficiencies of dicumarol therapy?**—As far as is known, dicumarol has no effect on a thrombus or embolus that is already present. It is used for the prevention of new thrombosis or extension of existing thrombosis and since emboli arise from fresh thrombi only, the prevention of fresh thrombosis will prevent embolism. The effect

of dicumarol is delayed for a day or more after it is administered and during this period the patient is not protected against thrombosis. The zone of effective and safe prothrombin deficiency produced by dicumarol is rather narrow (10 per cent to 30 per cent prothrombin) and the administration of dicumarol requires close observation of the patients and daily prothrombin time tests, therefore it is a rather unpractical method of preventing thrombosis for long periods (more than three months). Protection against thrombosis and therefore embolism ceases after the prothrombin deficiency induced by dicumarol ceases. There is the small risk of bleeding during the period of activity of the drug.

What is the best and simplest way to obtain a rapid anticoagulant antithrombotic effect and maintain it during a prolonged period?—Heparin injected intravenously will produce a rapid anticoagulant effect but it is impractical to use heparin for long periods because of its cost and the necessity for continuous or repeated intravenous administration. However, heparin can be administered during the few days between the time of administration of the first dose of dicumarol and the development of adequate prothrombin deficiency. The simplest method is to start the administration of heparin and dicumarol simultaneously giving 50 mg of heparin intravenously every four hours and giving the dicumarol according to the plan noted previously. As soon as the prothrombin is less than 20 per cent of normal the heparin may be discontinued. Prothrombin time tests to determine when this point is reached should be done at the end of the four-hour period after an injection of heparin and before the next dose of heparin is administered.

What are contraindications to the use of dicumarol?—Dicumarol is contraindicated in (1) the presence of definite renal insufficiency, because renal insufficiency greatly prolongs and increases its effect, (2) the presence of definite hepatic insufficiency for the same reason, (3) purpura of any type because of the danger of bleeding when capillary weakness and impaired coagulation are both present, (4) subacute bacterial endocarditis because of the vascular weakness caused by the disease and therefore increased liability to hemorrhage, (5) blood dyscrasia with tendency to bleed and (6) recent operation on the brain or spinal cord because of the grave consequence of even slight bleeding at the operative site. Dicumarol should be given cautiously to patients who have (1) ulcerative lesions, open wounds or potentially bleeding surfaces, (2) vomiting due to gastric or intestinal obstruction, (3) continuous or repeated gastric or intestinal drainage or (4) known dietary or nutritional deficiency. If patients are vomiting or have continuous or intermittent gastric or intestinal drainage by tube it may be futile to give dicumarol because the drug is absorbed poorly if at all.

What are the indications for the use of dicumarol?—Experience at the Clinic has indicated that the anticoagulant action of dicumarol is of

value in the following conditions (1) nonfatal postoperative, postinfectious or posttraumatic pulmonary embolism, because of the great risk of subsequent venous thrombosis and embolism during the subsequent few days or few weeks, (2) postoperative, postinfectious or posttraumatic thrombophlebitis because of the danger of extending or remote venous thrombosis and therefore of pulmonary embolism both fatal and nonfatal during the subsequent few days or few weeks, (3) after operations on patients who have previously had thrombophlebitis or pulmonary embolism because of the danger of recurrence of these complications, (4) after peripheral arterial embolism because of the danger of further intracardiac thrombosis and of propagating thrombosis from the embolus when the arterial spasm relaxes and (5) after acute peripheral arterial thrombosis from any cause because of the imminent danger of extending arterial thrombosis

Dicumarol may also be of value for patients who have thrombophlebitis or pulmonary embolism complicating blood dyscrasias or congestive heart failure, although there is a limit to the time that the anticoagulant effect can be maintained in these conditions and the thrombosing tendency may be prolonged. For the same reason dicumarol is of less value in recurrent idiopathic thrombophlebitis but during periods when the episodes recur with great frequency and may be interspersed with pulmonary infarcts, it may be advisable to use dicumarol. In postpartum thrombophlebitis or pulmonary embolism dicumarol should be used with caution although there is minimal risk of uterine bleeding if the uterus is normally involuted and if administration of the drug is not begun until the first postpartum week has elapsed.

In patients who have a large pulmonary embolism or acute peripheral arterial occlusion it is advisable to secure a rapid anticoagulant effect and to use preliminary heparinization as well as dicumarol. In cases of thrombophlebitis or in cases in which the drug is used for prophylactic purposes, preliminary heparinization is not necessary.

#### REFERENCES

- 1 Allen, E. V., Barker, N. W. and Waugh, J. M. A preparation from spoiled sweet clover [3,3'-methylene-bis-(4-hydroxycoumarin)] which prolongs coagulation and prothrombin time of the blood: a clinical study. *J. A. M. A.* 120:1009-1015 (Nov. 28) 1942.
- 2 Barker, N. W. The use of dicumarol in surgery. *Minnesota Med.* 27:102-106 (Feb.) 1944.
- 3 Barker, N. W., Nygaard, K. K., Walters, Waltman and Priestley, J. T. A statistical study of postoperative venous thrombosis and pulmonary embolism I. Incidence in various types of operations. *Proc. Staff Meet., Mayo Clin.* 15:769-773 (Dec. 4) 1940.
- 4 Barker, N. W., Nygaard, K. K., Walters, Waltman and Priestley, J. T. A statistical study of postoperative venous thrombosis and pulmonary embolism III. Time of occurrence during the postoperative period. *Proc. Staff Meet., Mayo Clin.* 16:17-21 (Jan. 8) 1941.

- 5 Bingham, J B., Meyer O O and Pohle F J Studies on the hemorrhagic agent 3,3-methylenebis (4-hydroxycoumarin) I Its effect on the prothrombin and coagulation time of the blood of dogs and humans. *Am J M Sc.* 202 563-578 (Oct.) 1941
- 6 Butt, H R., Allen E. V and Bollman J L. A preparation from spoiled sweet clover [3,3-methylene-bis-(4-hydroxycoumarin)] which prolongs coagulation and prothrombin time of the blood preliminary report of experimental and clinical studies. *Proc. Staff Meet., Mayo Clin* 16 388-395 (June 18) 1941
- 7 Campbell H. A. and Link, K. P. Studies on the hemorrhagic sweet clover disease IV The isolation and crystallization of the hemorrhagic agent. *J Biol Chem.* 138 21-33 (Mar) 1941
- 8 Cromer, H E., Jr and Barker N W. The effect of large doses of menadione bisulfite (synthetic vitamin K) on excessive hypoprothrombinemia induced by dicumarol. *Proc. Staff Meet., Mayo Clin* 19 217-223 (May 3) 1944
- 9 Hurn, Margaret, Barker N W and Magath T B. Prothrombin time determinations following the administration of dicumarol, with special reference to the variability of thromboplastin. *Proc. Staff Meet., Mayo Clin.* 19 507-512 (Oct. 18) 1944
- 10 Magath, T B., Technic of the prothrombin time determination. *Am. J Clin Path (Tech Suppl)* 3 187-189 (Sept.) 1939
- 11 Quick, A. J., Stanley Brown, Margaret and Bancroft, F W. A study of the coagulation defect in hemophilia and in jaundice. *Am J M Sc.* 190 501-511 (Oct.) 1935
- 12 Spooner Maryloo and Meyer O O. The effect of dicumarol 3,3-methylene-bis [4-hydroxycoumarin] on platelet adhesiveness. *Am J Physiol* 142 279-283 (Sept.) 1944
- 13 Stahmann, M. A., Huebner C. F and Link K P. Studies on the hemorrhagic sweet clover disease. V Identification and synthesis of the hemorrhagic agent. *J Biol. Chem* 138 513-527 (Apr) 1941

# CLINICAL SIGNIFICANCE OF THE ERYTHROCYTE SEDIMENTATION RATE

DONALD R. NICHOLS

THE erythrocyte sedimentation test is being used rather extensively throughout this country as a routine diagnostic procedure. Its value as a routine procedure has been stressed by numerous investigators. Cutler<sup>4</sup> reported that the test was of distinct diagnostic value in diseases characterized by disturbed stability of the blood. Schattenberg<sup>10</sup> advocated the erythrocyte sedimentation rate as a routine test in life insurance examinations. Gallagher<sup>6</sup> felt that the test could be used as a valuable part of health examinations of school children. Wintrobe<sup>12</sup> used the test as a routine procedure in the diagnostic clinic at Johns Hopkins Hospital. Agnor<sup>1</sup> reported the use of the test as a routine laboratory procedure in the Joseph H. Pratt Diagnostic Hospital. Reports by many other men from many other clinics have indicated that the test is being used widely in diagnostic centers and dispensaries and in the offices of individual physicians.

Helm<sup>8</sup> recently has suggested that perhaps the sedimentation rate is being used too routinely in general medical practice. The value of the test in determining the prognosis and progress of disease has been questioned.<sup>3</sup> There seems to be one point on which most investigators agree, however, namely, that the test is of definite value in indicating the presence of organic disease. Not infrequently, even before the disease can be recognized by the other usual clinical and laboratory methods, the presence of disease is suggested by an increased sedimentation rate.

The test is nonspecific and is of little value in distinguishing different diseases. It appears that the sedimentation rate varies with the amount of cellular destruction going on in the body.<sup>5</sup> When the amount of destruction of tissue passes beyond the normal, the stability of the blood is seriously disturbed and the erythrocytes settle out quickly from the plasma. The preponderance of evidence indicates that there is a direct correlation between the concentration of fibrinogen in the plasma and the sedimentation rate of the erythrocytes. Serum globulin seems to have a definite effect, at times, and there is some evidence that the concentration of cholesterol in the plasma influences the sedimentation rate.<sup>7</sup>

The simplicity of the test is one of its greatest assets. The technique is very simple, no elaborate equipment is needed and the results are known within an hour. A modified Westergren method of determining the sedimentation rate is widely used.<sup>1, 2</sup> The only special apparatus required is a Westergren tube and rack. It is also convenient to use a *e* with a mark indicating 5 c c. This may be a graduated centrifuge

tube or a plain test tube with a mark at the 5 c.c. level. The only reagent necessary is a 3.8 per cent solution of sodium citrate. The following technic is found to be satisfactory. Five-tenths cubic centimeter of a 3.8 per cent solution of sodium citrate in distilled water is placed in a tube, and to this is added 4.5 c.c. of venous blood. After the tube has been inverted several times to insure mixing, a Westergren tube is filled to the 200 mm. mark in a strictly vertical position at room temperature. The height of the column of plasma in the Westergren tube is read at the end of one hour and reported in terms of millimeters of sedimentation in one hour. In order that the test be accurate, certain factors must be emphasized. The tube must be absolutely vertical, the glassware must be clean, the test must be done within three hours after collection of the blood, and the temperature should be between 20° and 25° C.

With this method the normal sedimentation rate of men's erythrocytes is from 0 to 15 mm. in one hour, and the normal rate for healthy women is from 0 to 20 mm. Slightly elevated sedimentation rates are caused by so many factors that their significance is questionable. It is only when the sedimentation rate exceeds 30 mm. per hour that much importance can be attached to it.

When the sedimentation rate is used as a routine diagnostic test, certain problems arise in the interpretation of the results. A full consideration of all the diseases associated with an elevated sedimentation rate is beyond the scope of this paper. Fundamentally, any condition which produces significant destruction of tissue will cause an increased sedimentation rate,<sup>4, 8, 12</sup> therefore, most acute and chronic infections, malignant lesions, acute intoxications and certain endocrine disturbances will be associated with an abnormal rate. A careful history and physical examination usually will reveal or suggest the cause for the elevated rate. Confirmatory laboratory tests may be necessary.

Not infrequently, however, a markedly elevated sedimentation rate will be found in a case in which there is no objective organic disease. The problem then is to determine, if possible, the cause for the elevation of the rate. The explanation may be found by means of other routine laboratory tests. It is the custom in most diagnostic clinics to do routine urinalyses and to make blood counts. Serologic tests for syphilis are also usually a routine procedure. If the sedimentation rate is being used as an office procedure and these tests have not been carried out, an erythrocyte count is the first procedure indicated, inasmuch as anemia will cause an increase in the sedimentation rate. A leukocyte count will indicate the presence of relatively severe infections or blood dyscrasias, urinalysis will disclose whether or not there is an infection of the urinary tract, and serologic tests for syphilis are indicated inasmuch as an elevated sedimentation rate will almost always be found when active syphilitic lesions are present.<sup>11</sup> Roentgenologic examination of the thorax certainly is indicated, as the sedimentation

tion rate has been shown to be a very sensitive indicator of active pulmonary tuberculosis and of nontuberculous processes in the lungs. Physical examination of the thorax often will fail to reveal these lesions. When the history, physical examination and the previously mentioned laboratory procedures fail to reveal any evidence of organic disease, the problem of accounting for the elevated sedimentation rate becomes definitely more difficult.

In one of the general medical sections at the Clinic, the sedimentation rate has been performed as a routine diagnostic procedure. Because of rather general agreement that an elevation of the sedimentation rate usually indicates the presence of disease, careful study has been given to those cases in which there is a high rate but in which the

TABLE 1—OBSCURE DISEASES OFTEN ASSOCIATED WITH AN ELEVATED SEDIMENTATION RATE

- I Generalized infection
  - A Atypical rheumatic fever
  - B Early rheumatoid spondylitis
  - C Fungous infection, such as abdominal actinomycosis
  - D Parasitic infection, such as malaria in the apyrexial stage
- II Localized infections
  - A Abscess of the liver
  - B Tuberculosis of bone
- III Malignant lesions
  - A Carcinoma of the pancreas
  - B Carcinoma of the liver
  - C Hypernephroma
  - D Carcinoma of the prostate gland
  - E Multiple myeloma
- IV Lymphoblastoma
- V Acute intoxications, such as lead poisoning
- VI Endocrine disorders, such as early Addison's disease
- VII Vascular occlusion or inflammation, such as a mild, rather silent type of coronary occlusion
- VIII Diseases of the liver, such as cirrhosis

results of physical examination and routine laboratory tests are essentially negative. The routine laboratory tests which customarily are made include a leukocyte count, erythrocyte count, hemoglobin determination, urinalysis, flocculation test for syphilis, and a roentgenologic examination of the thorax. The history often is helpful in establishing the diagnosis. At other times, however, even the history is non-contributory.

In interpreting the significance of a markedly elevated sedimentation rate it must be remembered that the sedimentation rate returns to normal only very slowly. Moen and Reimann<sup>9</sup> have pointed out that normal rates usually are not obtained before one to two months after the acute phase of pneumonia. Ham and Curtis have shown that a single injection of typhoid vaccine will cause elevation of the rate as long as ten days. Markedly elevated rates will often be found

two months after clinical recovery from severe septicemia. Therefore, elevated sedimentation rates are of no significance in cases in which the patients have had a severe acute infection in the preceding weeks. Furthermore, when an elevated sedimentation rate is found, the test should be repeated after a period of time. This will serve as a safeguard against laboratory errors. Moreover, much more importance should be given to a sedimentation rate which is increasing or which remains markedly elevated than to one which is steadily approaching normal.

Table 1 lists some of the rather obscure diseases which may cause a marked elevation of the sedimentation rate. In this group of diseases the results of physical examination and routine laboratory tests may be negative and the history may not be diagnostic. The sedimentation rate may be markedly elevated.

There are undoubtedly many other diseases which could be added to this table. However, this classification will serve as a guide to some of the obscure or occult diseases which are often associated with an elevated sedimentation rate.

#### REPORT OF CASES

I shall report two cases which illustrate the value of the sedimentation rate as a routine procedure and the attention which must be paid to an elevated sedimentation rate.

**CASE 1.**—The patient was a white man forty-nine years of age. He was first seen at the Clinic on March 26, 1942. His chief complaints were of chronic fatigue and recurrent episodes of severe dizziness. He had had no episodes of true vertigo. The results of physical examination, including a complete neurologic examination, were essentially negative, except for a mild chronic prostatitis. The blood pressure was 110 mm. of mercury systolic and 70 mm. diastolic. The value for the hemoglobin was 13.1 gm per 100 c.c. of blood. The erythrocyte count was 4,620,000. The leukocyte count was 8,400 and the differential count was normal. A flocculation test for syphilis was negative. Urinalysis did not reveal any abnormality. Roentgenograms of the thorax revealed calcification of the pleura at the base of the right lung but were otherwise normal. A roentgenogram of the head was normal. The sedimentation rate determined by the Westergren method was 60 mm at the end of one hour.

In view of the negative results of physical examination and laboratory tests, the symptoms would have been considered functional in nature if it had not been for the high sedimentation rate. He was therefore kept under observation and typical Addison's disease developed subsequently.

**CASE 2.**—The patient was a white man fifty-seven years of age. He was first seen at the Clinic in April 1942. He gave a history of recurrent attacks of low back pain. There had been no sciatic extension of the pain and coughing had not aggravated the distress. Changes in the weather had no effect, and there was no stiffness noted on arising. The results of physical examination were essentially negative. Motions of the back were normal. The leukocyte count was 5,300 and the value for the hemoglobin 13.1 gm per 100 c.c. of blood. Urinalysis did not reveal any abnormality. Roentgenologic examination revealed narrowing of the



fourth and fifth lumbar interspaces, but otherwise did not disclose any abnormality. The value for the blood urea was 30 mg per 100 c c. The value for the serum phosphatase was 12 Bodansky units. The sedimentation rate determined by the Westergren method was 59 mm in one hour on one occasion and 67 mm on another.

The patient was suspected of having a protruded intervertebral disk, but there was little objective evidence for such a diagnosis. The high sedimentation rate indicated the presence of some active disease. However, there was no evidence of a spondylitis. In spite of extensive investigation, a definite diagnosis could not be reached, and it was felt that the patient should be kept under observation. Subsequent examinations later revealed the presence of multiple myeloma. This man's trouble would have been considered purely mechanical in nature if the markedly elevated sedimentation rate had not been found.

#### COMMENT

In both of these cases the sedimentation rate played a very significant role in indicating the presence of disease, although the results of physical examination and other laboratory tests were negative.

As stated previously, certain laboratory procedures are indicated when a high sedimentation rate is encountered and the disease is obscure. A leukocyte count, an erythrocyte count, a urinalysis, a flocculation test for syphilis and a roentgenologic examination of the thorax are essential. If the results of these tests are negative, certain other laboratory tests may at times be of value.

Determination of the concentration of serum protein often will reveal some gross abnormality in the protein metabolism and will serve as a lead to the diagnosis. For example, an excessively high concentration of serum globulin is suggestive of multiple myeloma.

Determination of the alkaline and acid phosphatase level in the blood occasionally will indicate the presence of a metastatic malignant lesion.

A liver function test may at times be indicated, inasmuch as cirrhosis of the liver or metastatic lesions in the liver occasionally cause a markedly elevated sedimentation rate.

Examination of special blood smears often will give information which is very helpful in establishing the diagnosis of an obscure disease.

Electrocardiographic findings in the presence of an elevated sedimentation rate occasionally will establish the diagnosis of coronary occlusion when the history is not diagnostic.

Even in spite of careful study, there will be an occasional case in which no adequate explanation for the increased sedimentation rate can be found. In such instances, the physician must rely on his clinical judgment and not become confused by the results of a single laboratory test. However, it should be remembered that repeated studies have consistently shown that an elevated sedimentation rate is usually a sign of the presence of organic disease. Therefore, when possible, it is wise to keep in touch with a patient who has an elevated sedimentation rate but no other evidence of organic disease, until the rate has

returned to normal or the cause for the elevation of the rate has become apparent.

### SUMMARY

The erythrocyte sedimentation rate is a simple test which can be used effectively as a routine diagnostic procedure in office practice as well as in large clinics. Its greatest value when it is used as a routine procedure is that it may call attention to obscure or occult diseases before these diseases can be recognized by the usual clinical and laboratory methods. A complete history, physical examination and certain other laboratory tests are indicated in those cases in which a high sedimentation rate is found and in which no specific disease is evident.

### REFERENCES

- 1 Agnor E. B. The blood sedimentation test as a routine diagnostic procedure—a clinical evaluation of 2063 cases. *Ann. Int. Med.* 14 774-788 (Nov.) 1940
- 2 Bannick, E. G., Gregg R. O. and Guernsey C. M. The erythrocyte sedimentation rate—the adequacy of a simple test and its practical application in clinical medicine. *J.A.M.A.* 109 1257-1262 (Oct. 16) 1937
- 3 Banyai A. L. and Cadden, A. V. Limitations of the erythrocyte sedimentation test in tuberculosis. *Arch. Int. Med.* 72 245-249 (Aug.) 1943
- 4 Cutler J. W. The practical application of the blood sedimentation test in general medicine—observations based upon approximately 5000 patients over a period of six years. *Am. J. M. Sc.* 183 643-657 (May) 1932
- 5 Fåhræus Robin. The suspension stability of the blood. *Physiol. Rev.* 9 241-274 (Apr.) 1929
- 6 Gallagher J. R. The value of the blood sedimentation test in the routine medical examination of adolescents and in certain of their diseases. *Am. J. M. Sc.* 188 450-455 (Oct.) 1934
- 7 Ham, T. H. and Curtis, T. C. Sedimentation rate of erythrocytes—influence of technical, erythrocyte and plasma factors and quantitative comparison of 5 commonly used sedimentation methods. *Medicine* 17 447-517 (Dec.) 1938
- 8 Helm, J. D., Jr.. The predictability of the character (increased or normal) of the erythrocyte sedimentation rate—a survey of 1000 cases. *Am. J. M. Sc.* 205 241-246 (Feb.) 1943
- 9 Moen J. K. and Reimann H. A. Plasma protein changes and suspension stability of the blood in lobar pneumonia. *J. Clin. Investigation* 12 589-598 (May) 1933
- 10 Schattenberg H. J. Sedimentation test as a routine laboratory procedure—observations on eleven hundred persons. *Arch. Int. Med.* 50 569-573 (Oct.) 1932
- 11 Walton A. C. R. The erythrocyte sedimentation test—a clinical and experimental study. *Quart. J. Med.* 2 79-116 (Jan.) 1933
- 12 Wintrobe, M. M. The erythrocyte sedimentation test. *Internat. Clin.* 2 (series 46) 34-61 (June) 1936

# THE DIAGNOSIS OF RAYNAUD'S DISEASE

EDGAR A. HINES, JR

It is well recognized that symptoms and signs of disturbance of the peripheral circulation may occur in the absence of any demonstrable organic disease of the vascular system. Such disturbances have been thought to be on a functional basis and frequently have been considered as functional vascular disease. One form of functional vascular disease is that in which spasm of the arteries or arterioles produces changes in color of the skin. In some instances the arterial spasm is severe enough to produce marked pallor and even the waxy color of the so-called dead finger. In other instances the changes in the peripheral circulation are of such degree that only a bluish (cyanotic) discoloration results. It has long been known that even moderate exposure to cold or an emotional upset would produce vasospasm with color changes in the skin of the extremities of certain persons.

Raynaud first emphasized that functional disturbances in the peripheral circulation at times may become severe and that they occasionally result in changes in the integrity of the skin and even in symmetrical gangrene. He noted that changes in color of the skin of the extremities indicative of disturbances in circulation could occur in the absence of any evidence of occlusive arterial disease. He was not aware, however, that these vasospastic changes also could be induced by certain occlusive arterial diseases and that they might occur in many other conditions involving organic disease of the blood vessels, the nervous system or skin. Following Raynaud's description, many of the conditions associated with color changes in the skin of the extremities, including symmetrical gangrene of the members, were termed "Raynaud's disease." Hutchinson was the first to recognize clearly that Raynaud had not described a separate entity when he described the intermittent color changes occurring on exposure to cold and the symmetrical gangrene which sometimes was observed in association with these intermittent color changes. Hutchinson wrote, "all who have studied in any detail the cases which have been grouped together under the name of Raynaud's disease will admit that the time has arrived when they ought to be classified. They are not all alike nor do they all tend to the same result. It would be well indeed if we could cease to use the term Raynaud's disease and speak rather of Raynaud's phenomenon. The latter expression is capable of having assigned to it a clear and definite meaning, the former is not. The phenomena in question are those of acrotic asphyxia and are liable to variation at different times, being in many cases distinctly paroxysmal and are to be explained by reference to the influence of the nervous system upon the blood vessels. Many of the cases which

have been quoted as examples of Raynaud's disease are, however, complicated or even primarily induced by organic disease of the skin (scleroderma), the blood vessels or the heart."

Hutchinson, besides suggesting use of the term 'Raynaud's phenomenon' to connote the episodes of color change in the extremities, recommended the use of further terms to indicate the underlying cause of the phenomenon, for example "traumatic Raynaud's phenomenon."

By "Raynaud's phenomenon" is meant the occurrence of *intermittent* episodes due to a vascular disturbance either primary or secondary, resulting in color changes of the extremities, principally the fingers and toes and less frequently the hands, feet, nose and ears initiated by exposure to cold and less frequently by emotional or nervous strain and stress.

In a small group of cases in which Raynaud's phenomena are present, however, it is impossible to demonstrate, even after the lapse of several years, any occlusive arterial disease or, in fact, any cause for the functional vascular changes. To this group the term "Raynaud's disease" may still be applied.

#### CLINICAL DESCRIPTION

The typical history in Raynaud's disease is that of a young woman who first observed color changes of the type of Raynaud's phenomenon on exposure to cold. Usually the onset of such alterations in color is not striking, although in some instances they may be called dramatically to the patient's attention by an acute episode of pallor in one or two fingers on exposure to cold, the so called dead finger phenomenon. In the early stage of the disease, only the tips of the fingers of both hands are involved. Later, the changes in color of the skin involve more of the proximal parts of the fingers until, in the late stages, the modifications in color may extend back to involve the hands. The color changes may consist of cyanosis solely or pallor solely but more commonly the variation in color is in three phases pallor, cyanosis and rubor. Symptoms are worse in the cold season and better in the warm season. Pain is not a prominent symptom during the attack or in the interval between attacks. Paresthesia, however, does occur commonly during the attack and consists of numbness, tingling, burning, a feeling of tightness, a "pins and needles" sensation or a sticking sensation in the fingers. During the attack, the fingers are cold and in many instances there is actual diminution of sensory acuity. In some cases slight swelling of the involved fingers may occur and, in others, the swelling may persist even during the interval between the attacks.

In the progressive or advanced stages of Raynaud's disease the Raynaud's phenomenon may become disabling in its severity and frequency. The attacks may occur on exposure to a slightly cool environment and under almost any emotional stress, consequently even the

warmer weather of the summer season may afford little relief. In many instances, sclerodermatous changes of considerable degree may affect the skin of the involved parts and may result in considerable interference with the normal use of the extremity, particularly of the fingers. Although extensive gangrene does not occur, the gangrenous ulcerations on the tips of the digits may be persistent and may cause considerable pain and discomfort. In an occasional instance these lesions may become infected and it may be necessary to amputate the distal parts of the involved finger or fingers. I have never seen a lesion in Raynaud's disease necessitating the amputation of a toe or of more than a portion of a finger.

### DIAGNOSIS

If the term "Raynaud's disease" is to be continued in use, strict adherence to accepted criteria for diagnosis must be observed. The medical literature is greatly confused by many cases in which an incorrect diagnosis of Raynaud's disease has been made. Since it has become more widely recognized that symmetrical gangrene does not occur solely, or even usually, in Raynaud's disease, mistakes in the diagnosis of Raynaud's disease have become fewer.

Identification is relatively easy if the diagnosis of Raynaud's disease is made only in cases in which Raynaud's phenomenon occurs without evidence of secondary cause and in which it is bilateral. It should have existed long enough in each case for any secondary cause to have become evident before a final diagnosis of Raynaud's disease is made.

The criteria for making a diagnosis of Raynaud's disease may be summarized briefly as follows: (1) episodes of Raynaud's phenomenon excited by cold or emotion, (2) bilaterality of the Raynaud's phenomenon, (3) absence of gangrene or, if present, its limitation to minimal grades of cutaneous gangrene, (4) absence of any other primary disease which might be causal, such as occlusive arterial disease, cervical rib or organic disease of the nervous system and (5) history of symptoms being noticed for two years or longer.

The most important point in making the diagnosis is the elimination of any possible secondary factors which within reason may be the cause of Raynaud's phenomenon. It should be remembered that secondary Raynaud's phenomenon is much more common than Raynaud's disease.

### DIFFERENTIAL DIAGNOSIS

In making the differential diagnosis, inquiry should be made as to possible contact with heavy metals and ergot. The family history of similar disturbances affecting other members of the family also may be helpful. When Raynaud's phenomenon has been restricted to one finger or to one extremity for a long period, some secondary causative factor should be suspected. When Raynaud's phenomenon occurs

in a man, it should be suspected of being due to thrombo-angitis obliterans or to some other organic factor

In making a differential diagnosis of Raynaud's disease from other diseases the prime objective is to rule out occlusive arterial disease

**Thrombo-angiitis Obliterans (Table 1)**—A review of the literature of vascular disease soon indicates that the disease which is most commonly confused with Raynaud's disease is thrombo-angitis obliterans. Three reasons are mainly responsible: 1 The emphasis which Raynaud gave to the symptom of symmetric gangrene resulted in confusion in diagnosis and many cases in which some degree of occlusive arterial disease, usually thrombo-angitis obliterans, was present were considered to

TABLE —DIFFERENTIAL DIAGNOSIS OF RAYNAUD'S DISEASE, THROMBO-ANGIITIS OBLITERANS AND ARTERIOSCLEROSIS OBLITERANS

	Raynaud's Disease	Thrombo-angiitis Obliterans	Arteriosclerosis Obliterans
Sex	Females in 70 per cent of cases	Males in 98 per cent of cases	Males in 85 per cent of cases
Age of onset years	12 to 30	20 to 40	More than 50
Color changes Raynaud's phenomenon Postural color change	100 per cent of cases Absent	30 per cent of cases 100 per cent of cases	10 per cent of cases 100 per cent of cases
Gangrene (if present)	Limited to small areas of skin	Minimal to extensive	Minimal to extensive
Involvement of upper extremities	Almost all cases	40 per cent of cases	Rare
Involvement of lower extremities	Usual but less frequently than upper extremities	98 per cent of cases	100 per cent of cases
Symmetry	Bilateral and symmetrical	Asymmetrical but usually bilateral	Asymmetrical but usually bilateral
Peripheral arterial pulsations	Present	Impaired or absent	Impaired or absent
Calcified arteries	Absent	Usually absent	Usually present
Superficial phlebitis	Absent	40 per cent of cases	Absent
Acrosceleroderma	None or moderate	Absent	Absent

have been cases of Raynaud's disease in subsequent descriptions. 2 Raynaud's phenomenon often occurs in both the upper and lower extremities in the early stages of thrombo-angitis obliterans. 3 The symptoms of Raynaud's disease and of thrombo-angitis obliterans usually begin in early adult life.

The differential diagnosis between these two conditions is not unusually difficult. The difference in sex incidence alone should indicate the differential diagnosis in the majority of cases inasmuch as Raynaud's disease occurs largely among females and thrombo-angitis obliterans, largely among males. In thrombo-angitis obliterans one extremity is usually involved first, whereas in Raynaud's disease both

upper extremities are usually involved first Raynaud's phenomenon when present in association with thrombo-angitis obliterans, is likely to involve only one or two digits even in the late stages of the disease A history of recurring superficial phlebitis also should arouse suspicion of thrombo-angitis obliterans as this does not occur in Raynaud's disease The final diagnosis of thrombo-angitis obliterans can be made by the demonstration of permanent arterial occlusion which, if present, rules out the possibility that the patient under consideration has Raynaud's disease In an occasional case, particularly in cases of thrombo-angitis obliterans in which only the digital arteries are involved, an arteriogram is necessary in order to demonstrate the presence or absence of occlusive arterial disease

**Arteriosclerosis Obliterans (Table 1)**—Raynaud's phenomenon rarely occurs in its typical form in arteriosclerosis obliterans and, when it does occur, usually only one or two digits are involved and usually pallor is an outstanding feature, with cyanosis being minimal or absent Age and sex are of great significance in consideration of a diagnosis of arteriosclerosis obliterans Raynaud's disease rarely begins in persons within the age limit in which arteriosclerosis obliterans occurs, namely, after fifty years of age Evidence of arteriosclerosis, of signs of other senile changes and of occlusive arterial disease, of course, will immediately point to a diagnosis of arteriosclerosis obliterans As in thrombo-angitis obliterans, the lower extremities are first and more extensively involved in arteriosclerosis obliterans, contrary to the involvement which occurs in Raynaud's disease In an occasional instance estimations of the fat in the blood are of value in differential diagnosis In arteriosclerosis obliterans the blood lipoids in many instances will be found to be elevated markedly whereas they are almost never markedly elevated in uncomplicated Raynaud's disease

**Acrocyanosis (Table 2)**—The sex and age of patients who have acrocyanosis and Raynaud's disease are similar Both diseases usually attack young women In acrocyanosis, however, the episodic nature of the color changes is not nearly so striking as it is in Raynaud's disease In acrocyanosis, the changes in color of the skin consist mostly in cyanosis which is of a diffuse nature and is more permanent than in Raynaud's disease Although the color changes in acrocyanosis may be increased by cold, there is often little effect from heat and vasodilatation Necrosis and ulceration of the finger tips sometimes occur in the late stages of Raynaud's disease, whereas such changes almost never occur in acrocyanosis

**Livedo Reticularis and Chronic Pernio (Table 2)**—Livedo reticularis easily is distinguished from Raynaud's disease by the *permanent*, reticulated pattern of the color changes These color changes usually involve all four extremities and sometimes the trunk, whereas, in Raynaud's disease, usually only the hands and feet are involved

Chronic pernio, a form of chilblains, is distinguished by the appearance, about and above the ankles, of typical, superficial skin lesions

TABLE 2 —DIFFERENTIAL DIAGNOSIS OF RAYNAUD'S DISEASE, ACROCYANOSIS, LIVEDO RETICULARIS, PERNIO AND ACROSCLEDERMIA

	Raynaud's Disease	Acrocyanosis	Livedo Reticularis	Pernio (erythrocyanosis)	Primary Scleroderma
Sex and age	Girls or young women in 70 per cent of cases	Girls or young women in 90 per cent of cases	Women or men, any age	Young women 70 per cent of cases	Young women 85 per cent of cases
Type of color change	Blue, red, white mottled or diffuse	Blue, diffuse	Red, blue, mottled and reticulated	Blue, red, localized	Blue, red, white mottled or diffuse
Location of vascular symptoms	Hands, feet, nose and ears rarely	Hands usually; feet occasionally	Legs usually; arms occasionally	Exposed surfaces, legs especially	Hands and feet
Duration of vascular symptoms	Intermittent	Permanent	Permanent	Variable; worse in winter	Intermittent
Local symptoms	Numbness or burning pain	None	None	Marked itching and burning	Stiffening and tension of skin
Effect of cold	Symptoms increased	Symptoms increased	Increased blueness	Causal increased redness	Symptoms increased
Effect of heat and vasodilatation	May decrease color changes greatly	Little change	Less blueness	More redness	May be decreased color changes
Effect of posture and exercise	Little change	Cyanosis decreased on elevation	Cyanosis decreased by elevation or exercise	No change	No change
Swelling	Slight or none	Slight or none	Slight or none	Slight or none	Slight to moderate
Necrosis and ulceration	Slight or limited or none	None	Occasionally in severe cases	Always in severe cases	Frequently in association with marked scleroderma



which appear in the cool seasons and disappear during the warm seasons. The patient suffering from chronic pernio may also have cold, cyanotic feet and hands, but, in the uncomplicated case, Raynaud's phenomenon does not occur.

**Acroscleroderma** (Table 2) —There is seldom any difficulty in distinguishing between the late stages of primary scleroderma and Raynaud's disease. However, in the early stages of primary scleroderma there may be considerable difficulty in determining whether the condition is the condition just named or Raynaud's disease. In attempting to establish the difference it is important to determine whether the Raynaud's phenomenon began before or after the onset of noticeable changes in the skin or periarticular tissues. If the Raynaud's phenomenon occurred before any changes in the skin were noted and if it has persisted for months or several years with only minimal sclerodermatous changes, then it is likely that Raynaud's disease is present. In the later stages of primary scleroderma the sclerotic changes involve the skin of the arms, face, chest and neck, these regions are not involved in the color changes. In Raynaud's disease, however, the changes in the skin occur only in or near the sites at which the color changes have been most marked, usually in the ends of the fingers or toes.

#### REFERENCES

- 1 Hutchinson, J. Raynaud's phenomena (Abstr.) *M. Press* n.s. 72 403-405, 1901
- 2 Raynaud, A.-G.-M. *De l'asphyxie locale et de la gangrène symétrique des extrémités*. Paris, Rignoux, 1862, 177 pp.

## THE EFFECT OF SMOKING CIGARETS AND THE INTRA VENOUS ADMINISTRATION OF NICOTINE ON THE HEART AND PERIPHERAL BLOOD VESSELS

GRACE M. ROTH, JOHN B. McDONALD\* AND CHARLES SHEARD

PERHAPS there is no more controversial subject today than the effects of smoking tobacco on the heart and peripheral blood vessels. There are many excellent papers on this subject but, in spite of all the comprehensive work, complete agreement among the various investigators is still lacking. For the most part this subject has been concerned with three major controversies: (1) whether the smoking of tobacco is an etiologic factor in organic circulatory disease, (2) whether vasoconstriction of the peripheral blood vessels takes place and to what degree as the result of smoking of tobacco, and (3) whether the effect is produced by the cigaret paper, the tobacco smoke, the nicotine or the mechanical act of smoking. In regard to the first controversy, experimental, clinical and statistical evidence has shown that smoking of tobacco most likely is only a contributory factor and not the exciting one.

The existence of vasoconstriction of the peripheral blood vessels may be determined by an increase in blood pressure and pulse rate, by a decrease of the cutaneous temperatures of the extremities or by a decrease of the velocity of blood flow of the peripheral vessels of the extremities as measured by the plethysmograph. Most investigators have agreed that an elevation of blood pressure and pulse rate occurs during smoking of tobacco. Definite vasoconstriction of the peripheral blood vessels as evidenced by a decrease of the cutaneous temperature of the extremities has been reported by Maddock and Coler,<sup>9</sup> Barker,<sup>1</sup> Wright and Moffat<sup>16</sup> and Lampson<sup>8</sup> and Moyer and Maddock.<sup>11</sup> With the exception of Mulinos and Shulman<sup>12</sup> the investigators generally have reported that smoking of tobacco causes a decrease of peripheral blood flow as measured by the plethysmograph. Mulinos and Shulman attributed the decrease in blood flow to deep breathing. Similarly Smithwick<sup>13</sup> reported a decrease in blood flow through the finger by immersion of the contralateral hand in cold water, by a loud noise or even by an unpleasant thought.

In regard to the precipitating factor which produces the vasoconstriction, Barker<sup>1</sup> in 1933 presented evidence that the effect of smoking on the peripheral blood vessels was due to the absorbed portion of the tobacco smoke and not to the cigaret paper. Other investigators have shown that the substances contained in tobacco smoke absorbed by the

---

Dr McDonald is Captain, Medical Corps, Army of the United States. Work done as a student officer while on assignment at the Mayo Foundation for instruction in internal medicine.

body are pyridine bases, carbon monoxide and nicotine. The pyridine compounds are irritating to the mucous surface and for the most part the amounts absorbed are too small to be of physiologic interest. Other investigators have found that the average saturation of carbon monoxide in the blood of smokers who inhaled was about 5 per cent in contrast to the 15 to 20 per cent saturation necessary to cause disagreeable symptoms in normal individuals. Maddock and Coller<sup>10</sup> and Moyer and Maddock presented evidence that the vasoconstriction produced by smoking standard cigarettes was analogous to that produced by the intravenous injection of a similar amount of nicotine contained in the standard cigarette. Furthermore, they, as well as Wright and others, noted that smoking cigarettes which did not contain nicotine produced no appreciable effects on the cutaneous temperature of the extremities. Goetz<sup>4</sup> in 1942 reported that the decrease in peripheral blood flow was first the result of reflexes due to the irritating effect of the smoke upon the mucosa of the lung and later due to the nicotine absorbed and accumulated during smoking. Haag<sup>5</sup> further supported the evidence of the role of nicotine when he demonstrated in animals that the rises of blood pressure occasioned by the intravenous injection of smoke solutions were proportional to their nicotine content.

In 1943, three interesting papers on smoking appeared. Johnston<sup>7</sup> in England added support to the nicotine theory in that he assumed that smoking of tobacco is essentially a means of administering nicotine. He felt that smokers showed the same attitude toward tobacco as addicts to a particular drug. He gave nicotine both hypodermically and intravenously and derived the same response as from the inhalation of tobacco smoke.

Weatherby<sup>14</sup> found that vasoconstriction took place after smoking standard cigarettes and when nicotine was removed from standard cigarettes and the denicotinized cigarettes were smoked the vasoconstriction was abolished almost completely. Restoration of the original nicotine content to such cigarettes restored the original effects, indicating that nicotine is the most important agent which contributes to the circulatory and cutaneous changes and not the altered respiratory movements associated with smoking, as suggested by Mulinos and Shulman. He also noted that when the subjects were ambulatory, vasoconstriction of the peripheral blood vessels did not occur during the smoking of standard cigarettes.

In contrast, Evans and Stewart<sup>2</sup> found a similar decrease in peripheral blood flow with reduction of the cutaneous temperature of the extremities as a result of smoking standard cigarettes, denicotinized cigarettes or cigarettes not containing any nicotine (corn silk). They attributed these changes to sympathetic stimulation brought about by the irritating effect of smoke upon the respiratory tract, and not to the nicotine content of the cigarettes. Thus the third controversy still exists. In addition, some investigators felt that habitual smokers devel-

oped a tolerance to tobacco and had little, if any, physiologic response to smoking

### PROCEDURE

Observations were made on four male physicians and two female technicians whose ages ranged from twenty-two to forty-one years. All were habitual smokers and inhaled during smoking. As they were accustomed to the procedure in the psychrometric room psychologic stimulation was at a minimum.

Standard cigarettes of different brands bought on the open market were used. As a control, cigarettes made of corn silk were smoked. Comparative studies with standard cigarette paper and French ashless cigarette paper were used with both standard cigarette tobacco (1 gm.) and corn silk to investigate the possibility of an irritating factor in the preparation or bleaching process of the paper. A popular British cigarette filter holder also was used with the standard cigarettes.

Data were obtained in a constant temperature room with an environmental temperature of 78° F (25.5° C.), with a relative humidity of 40 per cent. The subjects fasted for fifteen hours previous to the test, during the test they wore lightweight short pajamas and were in the supine position on comfortable beds.

The temperatures of the plantar surface of the first and third toes of both feet and the volar side of the distal phalanges of the first and third fingers of both hands were measured by means of copper-constantan thermocouples. In many instances mouth temperatures were noted before and after smoking and in several instances rectal temperatures were recorded simultaneously with those of the fingers and toes. When fairly constant readings of the cutaneous temperatures had been obtained and after the basal blood pressure and pulse rate had been determined, smoking was begun. Simultaneous determinations of the blood pressure, pulse rate and cutaneous temperature were obtained at intervals of one minute during the smoking period, which generally lasted about twelve to sixteen minutes. The subjects inhaled the tobacco smoke with their accustomed depth and frequency. The observations were continued for thirty minutes to one hour after smoking was discontinued. An attempt was made to avoid all unnecessary noise and other stimuli which might produce vasoconstriction during this period. In addition, a cold pressor test was done on each subject.

### RESULTS

Sixty-six observations were made on six normal subjects who were inveterate smokers and all of them inhaled. Unless otherwise stated the cutaneous temperature was measured while the subjects were resting in the supine position wearing lightweight short pajamas. When an unlighted cigarette was puffed for the period it usually took to smoke two standard cigarettes, there was little or no change of the cutaneous temperature of the extremities, of blood pressure or of the pulse rate.

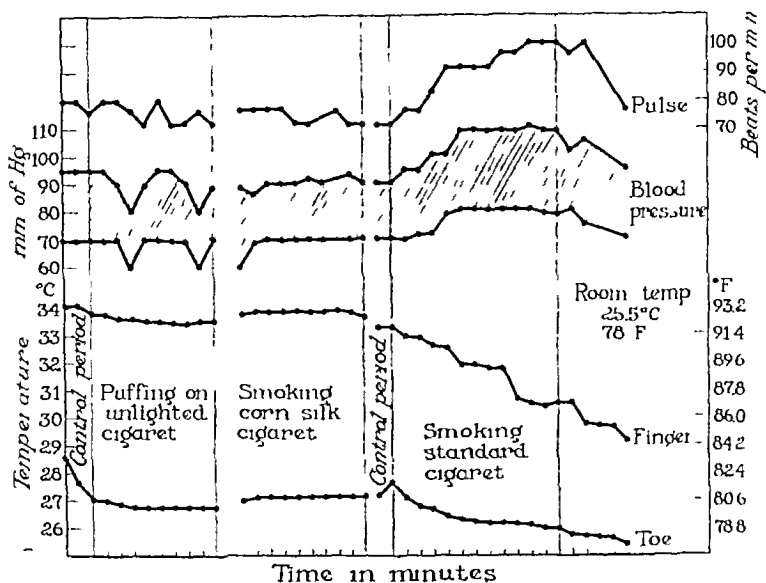


Fig 144—Effect of puffing on an unlighted cigaret, smoking two corn silk cigarets and smoking two standard cigarets on the cutaneous temperature of the extremities, blood pressure and pulse rate of the same subject. The cutaneous temperature curves of only one toe and one finger are shown. The control period in each instance was thirty minutes (Authors' article in J A M A., Vol 125 ,

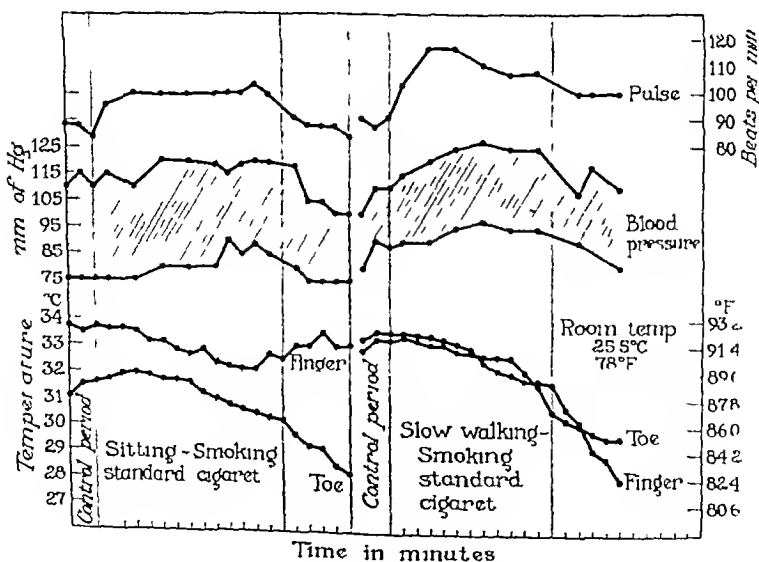


Fig 145—Effect of smoking two standard cigarets on the cutaneous temperature of the extremities the blood pressure and the pulse rate of the same subject while sitting and during slow walking. Note the decrease of the cutaneous temperature (Authors' article in J A M A., Vol 125 )

(fig 144) This was in accord with the findings of Evans and Stewart. When two corn silk cigarettes were smoked, there was a decrease of the cutaneous temperature in only two instances of  $0.1^{\circ}$  to  $0.7^{\circ}$  C. in the toes with a decrease of  $0.6^{\circ}$  to  $2.0^{\circ}$  in the fingers, and the blood pressure and pulse rate were practically unchanged (fig 144). The effect of smoking corn silk cigarettes was not irritating as evidenced by the absence of nasopharyngeal irritation and coughing. When two standard cigarettes were smoked there was an average decrease in the skin

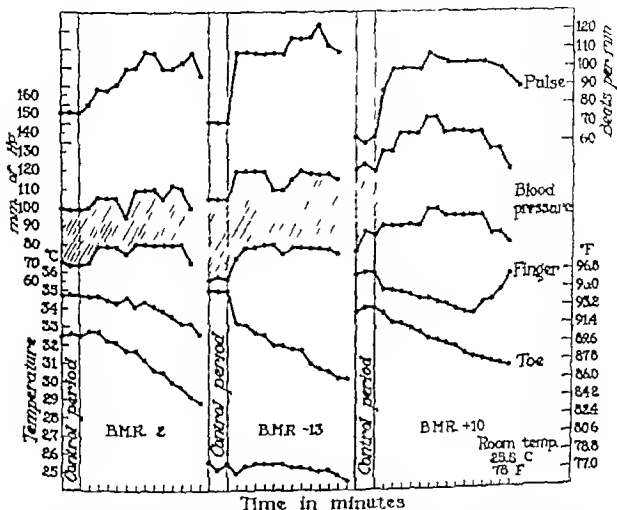


Fig 146.—Effect of smoking two standard cigarettes on the cutaneous temperature of the extremities, the blood pressure and the pulse rate of 3 normal subjects characterized by three different basal metabolic rates. When the basal metabolic rate is low the cutaneous temperature of the toes is correspondingly low when the basal metabolic rate is high the cutaneous temperature of the toes is high (Authors article in JAMA, Vol 125)

temperatures of the toes of  $1.8^{\circ}$  C. with a range of  $0.7^{\circ}$  C to  $4.3^{\circ}$  C. while in the fingers the average decrease was  $3.2^{\circ}$  C. with a range from  $1.2^{\circ}$  to  $6.5^{\circ}$  C. The greatest decrease in any one digit was  $4.3^{\circ}$  C. for the toes and  $7.7^{\circ}$  C. for the fingers.

When French ashless cigarette papers were used with the amount of tobacco in a standard cigarette or with corn silk, the effect on the cutaneous temperatures of the extremities, blood pressure and pulse rate corresponded to the effect produced by the respective cigarettes alone. The British filter holder together with standard cigarettes produced the same decrease in cutaneous temperature of the extremities

and the same increase of blood pressure and pulse rate as did the standard cigarettes alone

Since the criticism has been made that not many individuals smoked while in the supine position in bed, observations were made when the subject was fully clothed and in a sitting position and during slow walking. The thermocouples were placed inside the socks and shoes. Observations were first made during a thirty minute control period, then during the period when two standard cigarettes were smoked (fig 145). The decrease in the cutaneous temperature of the extremities was similar to that found under basal conditions and these results were contrary to those of Weatherby.

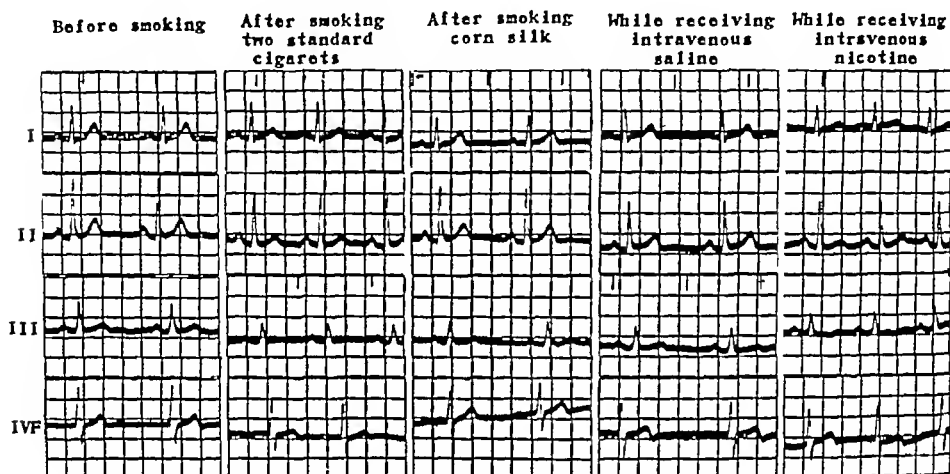


Fig 147—Electrocardiographic tracings taken on the same subject on different days. In the tracings the heart rate is the same before smoking, after smoking corn silk and while physiologic salt solution was being administered intravenously, and the amplitude of the T waves does not vary more than from 0.5 to 1.0 mm. The heart rate after the subject had smoked two standard cigarettes was 100 beats per minute, while the subject was receiving nicotine intravenously the rate was 110 beats per minute. The amplitude of the T waves decreased about 1 mm more as the result of intravenous administration of nicotine than during the smoking of two standard cigarettes. There was a definite decrease both from smoking two standard cigarettes and from the intravenous administration of nicotine, averaging between 1 and 3 mm (Authors' article in JAMA, Vol 125).

As has been previously shown, there is a more or less linear relationship between the skin temperature of the toes and the basal metabolic rate. When two standard cigarettes were smoked, the decrease in the skin temperature of the toes was partially dependent upon whether the basal metabolic rate was low or high. The different decreases in the skin temperature of the toes and the fingers with various basal metabolic rates are shown in figure 146. Furthermore, the basal metabolic rate increased with the smoking of two standard cigarettes and decreased with the smoking of two corn silk cigarettes by the particular subjects. These results are similar to those of Goddard and Voss<sup>3</sup> and Evans and Stewart, who found an increase in 69 per cent of their subjects.

The electrocardiographic tracing made before smoking in one case is shown in figure 147. All tracings made after smoking standard cigarettes had resulted in an increase of heart rate averaging between 16 and 36 beats per minute. A decrease in the amplitude of the T waves was noted in all subjects. The average decrease was between 1 and 2 mm in all leads and in a few instances the T wave in lead III became iso-electric. The greatest decrease in amplitude of the T waves was noted after the smoking of standard cigarettes. The tracings made after smoking corn silk showed no changes in amplitude of the T waves, the maximal decrease in amplitude of the T waves ranged be-

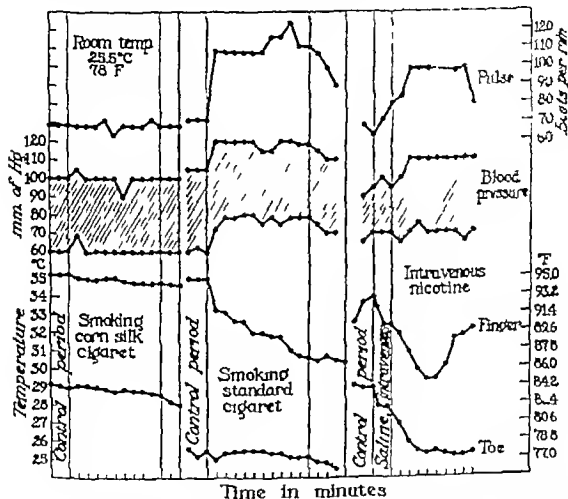


Fig 148—Effect of smoking two corn silk cigarettes, of smoking two standard cigarettes and of an intravenous injection of 2 mg of nicotine on the cutaneous temperature of the extremities, the blood pressure and the pulse rate of the same person. (Authors' article in J.A.M.A., Vol 125)

tween 0.5 and 1.0 mm, and in three instances there was a slight increase in amplitude of the T waves. Changes in amplitude of the QRS were negligible and in no instance was there an increase in the PR or the QRS intervals. Physiologic salt solution and nicotine also were administered intravenously. After basal tracings had been made an infusion of isotonic solution of sodium chloride was started. When basal tracings had been made under these circumstances without the patients being aware of the change, 2 mg of nicotine was given through the same apparatus. The electrocardiographic tracings made during the administration of physiologic salt solution resulted in no increase in



and the same increase of blood pressure and pulse rate as did the standard cigarets alone

Since the criticism has been made that not many individuals smoked while in the supine position in bed, observations were made when the subject was fully clothed and in a sitting position and during slow walking. The thermocouples were placed inside the socks and shoes. Observations were first made during a thirty minute control period, then during the period when two standard cigarets were smoked (fig 145). The decrease in the cutaneous temperature of the extremities was similar to that found under basal conditions and these results were contrary to those of Weatherby

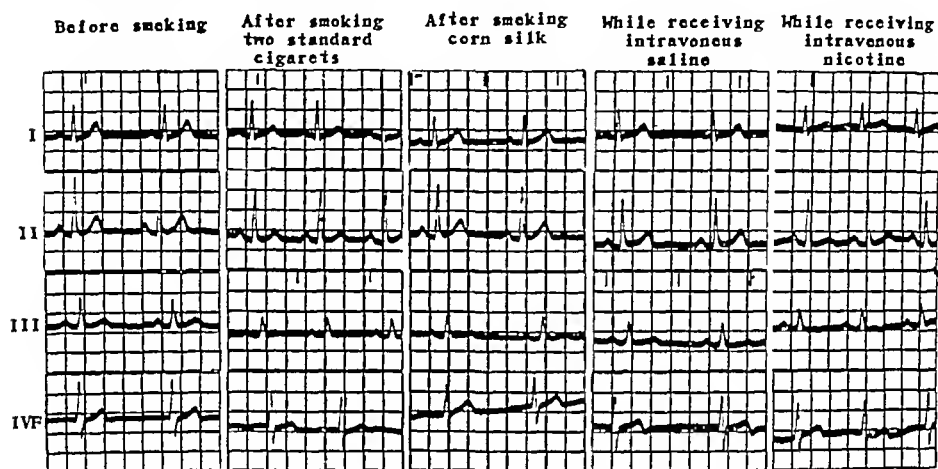


Fig 147—Electrocardiographic tracings taken on the same subject on different days. In the tracings the heart rate is the same before smoking, after smoking corn silk and while physiologic salt solution was being administered intravenously, and the amplitude of the T waves does not vary more than from 0.5 to 1.0 mm. The heart rate after the subject had smoked two standard cigarettes was 100 beats per minute, while the subject was receiving nicotine intravenously the rate was 110 beats per minute. The amplitude of the T waves decreased about 1 mm. more as the result of intravenous administration of nicotine than during the smoking of two standard cigarettes. There was a definite decrease both from smoking two standard cigarettes and from the intravenous administration of nicotine, averaging between 1 and 3 mm. (Authors' article in JAMA, Vol 125)

As has been previously shown, there is a more or less linear relationship between the skin temperature of the toes and the basal metabolic rate. When two standard cigarettes were smoked, the decrease in the skin temperature of the toes was partially dependent upon whether the basal metabolic rate was low or high. The different decreases in the skin temperature of the toes and the fingers with various basal metabolic rates are shown in figure 146. Furthermore, the basal metabolic rate increased with the smoking of two standard cigarettes and decreased with the smoking of two corn silk cigarettes by the particular subjects. These results are similar to those of Goddard and Voss<sup>3</sup> and Evans and Stewart, who found an increase in 69 per cent of their subjects

The electrocardiographic tracing made before smoking in one case is shown in figure 147. All tracings made after smoking standard cigarettes had resulted in an increase of heart rate averaging between 16 and 36 beats per minute. A decrease in the amplitude of the T waves was noted in all subjects. The average decrease was between 1 and 2 mm. in all leads and in a few instances the T wave in lead III became iso-electric. The greatest decrease in amplitude of the T waves was noted after the smoking of standard cigarettes. The tracings made after smoking corn silk showed no changes in amplitude of the T waves, the maximal decrease in amplitude of the T waves ranged be-

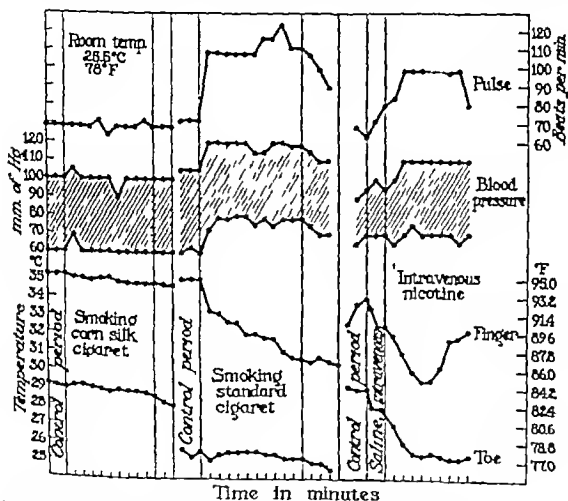


Fig 148—Effect of smoking two corn silk cigarettes, of smoking two standard cigarettes and of an intravenous injection of 2 mg of nicotine on the cutaneous temperature of the extremities, the blood pressure and the pulse rate of the same person. (Authors' article in J.A.M.A., Vol 125)

tween 0.5 and 1.0 mm., and in three instances there was a slight increase in amplitude of the T waves. Changes in amplitude of the QRS were negligible and in no instance was there an increase in the PR or the QRS intervals. Physiologic salt solution and nicotine also were administered intravenously. After basal tracings had been made an infusion of isotonic solution of sodium chloride was started. When basal tracings had been made under these circumstances without the patients being aware of the change 2 mg of nicotine was given through the same apparatus. The electrocardiographic tracings made during the administration of physiologic salt solution resulted in no increase in

the heart rate and in one instance in a decrease in the heart rate. There was either no change in the amplitude of the T wave or a maximal decrease of between 0.5 and 1.0 mm. After the intravenous administration of nicotine the tracings showed an average increase of heart rate of between 30 and 40 beats per minute. In all subjects there was an average decrease in amplitude of the T waves of between 1 and 3 mm in all leads and in a few instances the T waves demonstrated negativity in lead III. Changes in amplitude of the QRS were negligible and in no instance was there an increase in PR or the QRS intervals.

A comparison of the results of smoking corn silk cigarettes, smoking two standard cigarettes and an intravenous administration of nicotine was made on the same individual (fig. 148). With intravenous administration of physiologic salt solution for fifteen minutes previous to the injection of nicotine there was a slight decrease in the skin temperature of the extremities in two of the subjects. After the administration of 2 mg. of nicotine there was a sharp decrease in the skin temperature of the extremities in all subjects, at least parallel to that produced by two standard cigarettes.

While Hines and one of us (G. M. R.<sup>6</sup>) found an excessive rise of the blood pressure in patients with hypertension during smoking, in some normal individuals there may be a parallelism between hyper-reaction to the cold pressor test and hypersensitiveness to tobacco, in many other individuals hyper-reaction may be due to one or the other cause.

#### SUMMARY

This investigation was begun primarily to determine whether habitual smokers with normal blood pressure and pulse rate and normal vascular systems develop a tolerance to tobacco or demonstrate any physiologic changes as a result of smoking. Vasoconstriction in these subjects was evidenced by a decrease in the skin temperature of the extremities and an increase in blood pressure and pulse rate during smoking of two standard cigarettes. An increase in the basal metabolic rate and changes in the electrocardiographic tracings also took place. The blood pressure, pulse rate and electrocardiographic tracing was normal within five to fifteen minutes after the smoking ceased, while the peripheral vascular constriction, as evidenced by a decrease in skin temperature, persisted from a half to one hour. There was some variation in the degree of response to smoking in different individuals and in the same subject from day to day.

While most individuals smoke when sitting or walking, few observations have been made under these circumstances. Weatherby reported that mild physical activity inhibited the fall in skin temperatures of the extremities when smoking one cigarette. However, we found the same degree of vasoconstriction in our subjects who were fully clothed during the smoking of two cigarettes while sitting or walking slowly as when they were at rest under basal conditions.

Since vasoconstriction was not evident during the puffing of an unlighted cigaret, and during the smoking of corn silk cigarets, the mechanical effort of smoking was not a factor in the production of vasoconstriction. As Barker had previously stated, we found that various cigaret papers were not a factor in the production of vasoconstriction. This leaves the absorbed products of the tobacco to be accounted for. We had the opportunity of observing the effects of nicotine alone. We confirmed the observation of Maddock and Collier and Moyer and Maddock in regard to the peripheral vasoconstriction as evidenced by the decrease in skin temperatures and an elevation of blood pressure and pulse rate produced by both smoking of standard cigarets and by a similar amount of nicotine injected intravenously. In addition, we compared for the first time the effect of smoking standard cigarets and the intravenous injection of a similar amount of nicotine on the electrocardiographic tracings of the subjects and found them strikingly similar.

## REFERENCES

- 1 Barker, N. W. Vasoconstrictor effects of tobacco smoking. *Proc. Staff Meet., Mayo Clin.* 8:284-287 (May 10) 1933.
- 2 Evans, W. F. and Stewart, H. J. Effect of smoking cigarettes on peripheral blood flow. *Am Heart J.* 26:78-91 (July) 1943.
- 3 Goddard, V. R. and Voss, J. G. The immediate effect of cigarette smoking upon basal metabolic rates of university men and women. *J Lab & Clin Med.* 27:787-791 (Mar) 1942.
- 4 Goetz, R. H.: Smoking and thrombo-angitis obliterans. *Clin. Proc.* 1:190-203 (June) 1942.
- 5 Haag, H. B. The physiologic activity of cigarette smoke solutions as related to their nicotine content. *J Lab & Clin Med.* 25:610-618 (Mar) 1940.
- 6 Hines, E. A., Jr and Roth, Grace M. The effect of tobacco on the blood pressure as measured by a standard smoking test. *Proc. Staff Meet., Mayo Clin.* 13:524-526 (Aug 17) 1938.
- 7 Johnston, L. M. Tobacco smoking and nicotine. *Lancet* 2:742 (Dec 19) 1942.
- 8 Lampson, R. S. A quantitative study of the vasoconstriction induced by smoking. *J.A.M.A.* 104:1963-1966 (June 1) 1935.
- 9 Maddock, W. G. and Collier, F. A.. Peripheral vaso-constriction by tobacco demonstrated by skin temperature changes. *Proc. Soc. Exper. Biol. & Med.* 29:487-488 (Jan) 1932.
- 10 Maddock, W. G. and Collier, F. A.. Peripheral vasoconstriction by tobacco and its relation to thrombo-angitis obliterans. *Ann. Surg.* 98:70-81 (July) 1933.
- 11 Moyer, C. A. and Maddock, W. G. Peripheral vasospasm from tobacco. *Arch. Surg.* 40:277-285 (Feb) 1940.
- 12 Mulinos, M. G. and Shulman, Israel. The effects of cigarette smoking and deep breathing on the peripheral vascular system studied by five methods. *Am J. M. Sc.* 199:708-720 (May) 1940.
- 13 Smithwick, R. H. Surgical intervention on the sympathetic nervous system for peripheral vascular disease. *Arch. Surg.* 40:286-306 (Feb) 1940.
- 14 Weatherby, J. H. Skin temperature changes caused by smoking and other sympathomimetic stimuli. *Am Heart J.* 24:17-30 (July) 1942.
- 15 Wright, I. S. and Moffat, Dean. The effects of tobacco on the peripheral vascular system. *J.A.M.A.* 103:318-323 (Aug 4) 1934.

# IRON DEFICIENCY AND ANEMIA ASSOCIATED WITH CARCINOMA OF THE PROXIMAL PORTION OF THE COLON\*

R LEE CLARK, JR.,† MARSCHELLE H POWER, FRANK J HECK AND  
CLAUDE F DIXON

THE majority of opinions regarding anemia associated with carcinoma of the right portion of the colon have been based on the study of specimens long after they have been removed and stored in fixing solutions and after the histories have become unfamiliar. This study is based on the observation of patients while they were undergoing treatment for carcinoma of the right segment of colon.

The anemia produced by carcinoma of the proximal portion of the colon may be due to any one or a combination of the following: the carcinoma, the secondary infection, a toxin, metastasis, changes in the intestine secondary to obstruction, hemorrhage, or an iron deficiency.

Investigation of the concentration of iron in the serum of patients with carcinoma of the right half of the colon appeared to offer a different method of studying the anemia. Study of serum iron is necessary in view of the work of Moore, Doan and Arrowsmith,<sup>13</sup> which seemingly assigned the role of transporting iron to the serum. If the values for the serum iron are found to be abnormal, the concentration of the serum iron with other clinical, laboratory, and pathologic findings in a series of cases of carcinoma of the proximal portion of the colon might be of value in evaluation of the mechanism of production of the concurrent anemia.

## METHODS

The methods employed, both in collecting the samples of blood and in the laboratory procedures dealing with determination of the concentration of iron in the serum, were utilized essentially as described by Moore, Arrowsmith, Quilligan and Read.<sup>14</sup> Each estimate for the serum iron value was obtained by averaging the concentration in two samples of blood which were collected separately. Such a precaution afforded a check on the accuracy of the method used and reduced to a minimum the chances of error from contamination. In none of the cases was the variation greater than 10 micrograms per 100 c c, a variant within the limits of error for the technic utilized.

In addition to determinations of the concentration of serum iron,

---

\* An abridgment of a thesis submitted by Dr. Clark to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M.S. in Surgery.

† Since this paper was written Dr. Clark has joined the armed forces and is now Major, Medical Corps, Army of the United States.

this study included estimation of erythrocyte count, examination of blood smears and evaluation of the color index, volume index, saturation index and hematocrit readings. Additional laboratory investigations in certain instances included analysis of gastric contents, the determination of the sedimentation rate, reticulocyte count and concentration of bilirubin, and the van den Bergh reaction.

The concentration of hemoglobin was determined by the method of Sanford and Sheard,<sup>18</sup> using their photo electrometer. This instrument was standardized at frequent intervals by comparing results with those obtained by gasometric determinations for oxygen capacity of the blood as devised by Van Slyke and Neill.<sup>1</sup> The percentage of error was maintained below  $\pm 2.0$  per cent. The remaining procedures were in routine use in the laboratory and have been described in a recent standard treatise on laboratory technique.<sup>20</sup>

Clinical features bearing on the investigations have been considerations of age, sex, type and duration of symptoms and previous therapy. The pathologic data pertained to the size, grade, type and situation of the carcinoma and the frequency of its association with ulceration, metastasis, perforation, obstruction or other structural changes in the involved segment of colon.

## RESULTS

The studies herein reported were made on twenty-three patients with a carcinoma in some portion of the colon. Twenty-one of the twenty-three patients had a lesion involving the proximal portion of the colon. One of the remaining two patients had carcinoma of the splenic flexure and one had carcinoma of the rectosigmoid. Both patients had anemia and were included for purposes of comparison. An evaluation of the clinical features in each case was made in attempting to determine what factors could exert an influence on blood formation. No correlation between any particular symptom and the anemia could be made. However, it was observed that diarrhea, indigestion, anorexia, nausea or excessive pain was present, separately or combined, in practically all instances and that the nutritional status of the patient (average loss of weight 16.3 pounds) was greatly altered. It is readily conceivable that such disturbances could result in a decrease in the amounts of substances which are ordinarily eaten and absorbed and are available for combating anemia.<sup>11, 12</sup>

The age variant of the twenty-one patients who had carcinoma of the proximal portion of the colon (thirty-eight to seventy-two years) and the sex (ten women and eleven men) appeared to have no bearing on the degree or frequency of anemia. It was surprising how long symptoms had been present before the patients came for consultation. Fifteen of the twenty-one patients had had symptoms for one to two years or more. The frequency of occurrence of low concentration of hemoglobin increased with the duration of symptoms.

The occurrence of anemia in a case in which carcinoma is situated in the right half of the colon is not coincidental. Repeated reports<sup>1, 5, 15, 16</sup> of studies conducted on large series of patients attest to the occurrence of anemia in about 50 per cent of cases while only about 5 per cent of patients with a carcinoma in the left half of the colon have abnormal blood findings.

It has been demonstrated<sup>1</sup> that ulcerating carcinomas of the proximal portion of the colon are larger than those in the distal portion of the colon or in other hollow viscera.

The specific distribution of the cancerous process in the twenty-one consecutive cases of malignant lesions of the proximal portion of the colon studied was thirteen in the cecum, five in the ascending colon and three in the hepatic flexure.

It is of interest that the grade of activity<sup>3</sup> of the carcinoma cells was inversely proportional to the degree of anemia. That is, the most profound anemia was associated with a low grade of malignancy. The carcinomas of a low grade of activity had been present a longer time than those of a high grade of malignancy and prolonged surface hemorrhage could have brought about depletion of the iron reserves. Ulceration was present in nineteen of the cases and surface hemorrhages, usually of a degree which was not macroscopic in the feces, had undoubtedly occurred for a considerable time before resection. Obstruction is not a characteristic feature of malignant lesions of the proximal part of the colon and complete obstruction is very rarely encountered unless the growth has become so extensive that it involves the ileocecal valve. Complete blockage of fecal current had not occurred in any case in this series although in four instances the tumor had entirely encircled the lumen of the bowel and in a total of eight cases an obstructing tendency was manifest. The anemic trend in these cases was present before and not after symptoms of obstruction occurred. Likewise, studies by Welch, Mayo and Wakefield<sup>22</sup> have demonstrated that in cases in which malignant lesions were situated in the colon (involved the ileocecal valve) there were no histologic changes in the proximal and distal segments of the colon. Perforation should also be of interest in considering the various features capable of producing anemia as it adds the element of infection. A tendency to perforation was evident in seventeen of the cases as the carcinoma had penetrated the layers of the wall of the colon. However, infection arising from the perforation was of consequence in only one instance. In this case (case 16) a huge abscess developed in the right lower quadrant of the abdomen following ileocolostomy. Anemia had been present for some months previously and remained unchanged following the perforation.

Metastasis had occurred to the regional lymph nodes in nine of the cases, and liver in one case, and in another generalized dissemination of the cancerous process was demonstrated. The highest value for

hemoglobin (case 1) was found in conjunction with the most extensive local growth, regional metastasis and involvement of the liver. Metastatic carcinoma did not appear to affect any concurrent anemia.

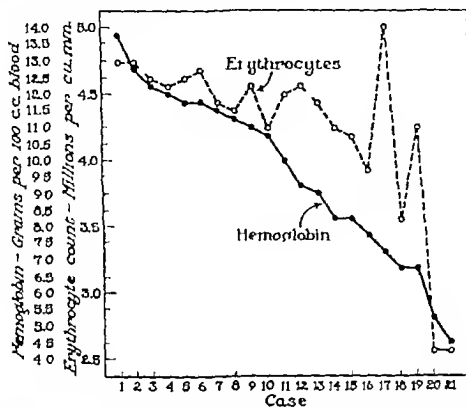


Fig. 149—Values for erythrocytes and hemoglobin in association with carcinoma of the right half of the colon

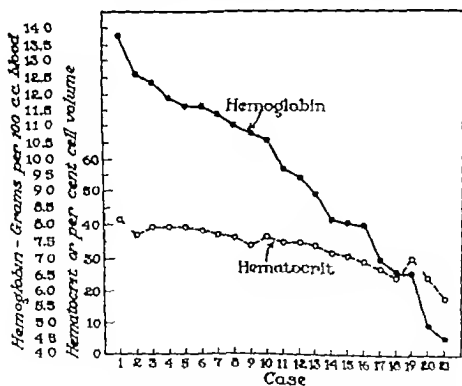


Fig. 150—Values for hemoglobin and hematocrits in association with carcinoma of the right half of the colon

Characteristically then, a low-grade, large, ulcerating penetrating nonobstructing carcinoma was found in association with metastasis in approximately 50 per cent of the cases. It appears significant that the



largest carcinomas of the colon and those that exist for the longest period before producing symptoms are situated in that part of the colon in which cancer is most frequently associated with anemia

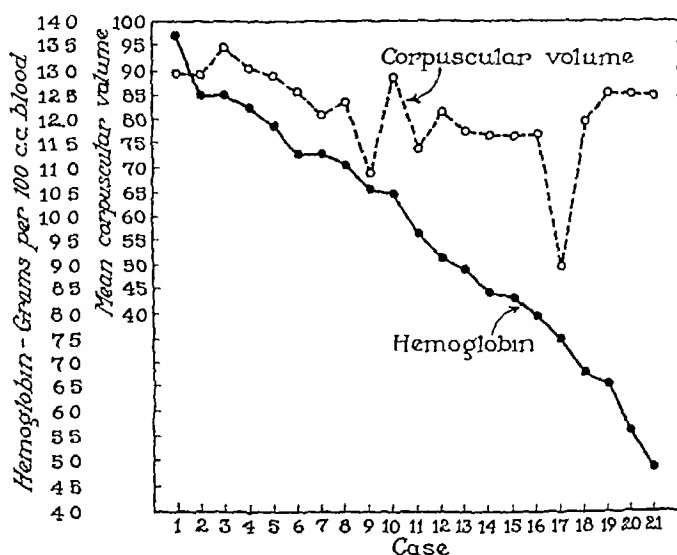


Fig 151—Values for mean corpuscular volumes and hemoglobin in association with carcinoma of the right half of the colon

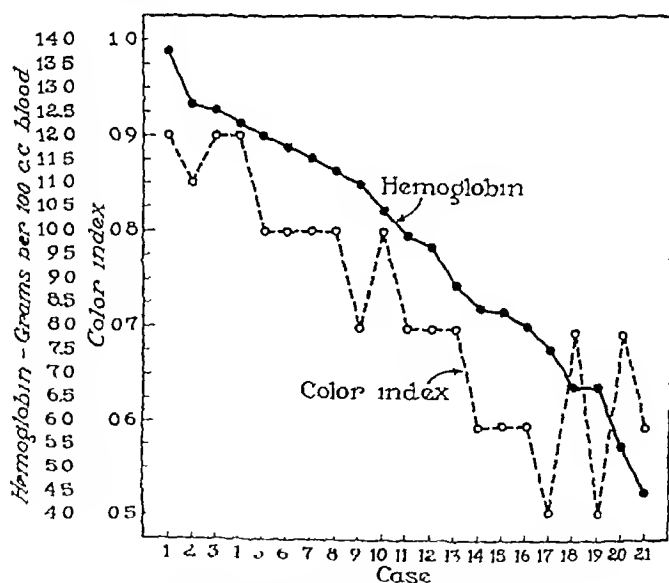


Fig 152—Values for hemoglobin and color index in association with carcinoma of the right half of the colon

**Characteristics of the Blood.**—In this series of cases (fig 149) the erythrocyte count was found to be high when the determinations were reviewed, being below four million in only three cases and in

each of these severe anemia was present. Hemoglobin deficiency was the outstanding feature of the blood picture (in thirteen cases the value for hemoglobin was less than 10 gm per 100 c.c. of blood) As would be expected from the comparative values for the erythrocytes and hemoglobin (fig 149) the morphologic features of the blood were characterized principally by a decrease in the hemoglobin of the erythrocytes. This hypochromasia varied from essentially normal cells to a marked decoloration as the values for the hemoglobin decreased. Of the twenty-one patients with lesions of the right colon, only two presented approximately normal blood pictures, nineteen exhibited slight to marked hypochromasia and nine showed varying degrees of microcytosis (figs 149 and 150). The microcytic character of the erythrocytes occurred in those instances in which the concentration

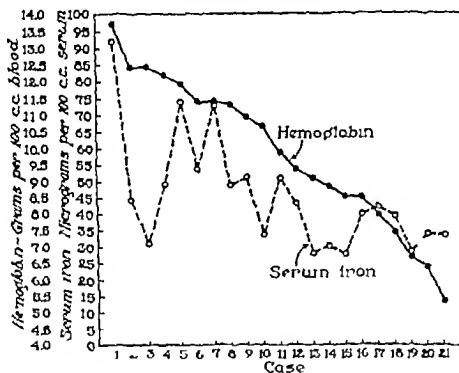


Fig 153—Values for hemoglobin and serum iron in association with carcinoma of the right half of the colon.

of hemoglobin was very much below normal. A typical severe anemia that accompanies carcinoma of the right segment of the colon may be classified as a hypochromic microcytic anemia (fig 150).

Other related blood findings were reticulocyte counts ranging from 0.5 to 1.5 per cent before treatment, hematocrit variations from low normal of 42 per cent to 27 per cent (fig 150), the decrease corresponding well to the decrease in hemoglobin. The volume index and mean corpuscular volume were below unity (fig 151) the disparity increasing as the degree of anemia became more profound and true microcytosis developed. A low color index was a characteristic feature (fig 152) and in five cases a slight to moderate 'left shift' of the polymorphonuclear leukocytes was the only other alteration of importance. There was no evidence in the circulating blood of hemolysis

and even in the presence of severe anemia the concentration of serum bilirubin and the van den Bergh reaction were normal. Essentially the same type of blood picture was present in the two cases in which the lesion occurred in the left half of the colon.

In attempting to correlate the association of a hypochromic microcytic anemia and carcinoma of the right half of the colon, the various causative factors of a hemoglobin deficiency anemia are to be considered. One of the most obvious essentials for elaboration of hemoglobin is iron. An iron deficiency results in a lowered concentration of hemoglobin and a decrease in the size of the erythrocytes.<sup>8</sup> Therefore, since the type of anemia encountered in these cases was one that is associated with a lack of iron, studies of complete iron metabolism suggest a mode for estimating the relationship of iron and anemia. However, even if complete studies of such a nature could be conducted on very ill patients, the data thus obtained would be circumstantial since the actual quantity of iron absorbed and excreted could

TABLE 1—AVERAGE BLOOD FINDINGS IN TWENTY-ONE CASES OF CARCINOMA OF THE COLON AND IN FIVE NORMAL PERSONS

Status	Hemoglobin, gm. per 100 c.c	Erythrocytes, millions per cu. mm	Hematocrit Reading, per cent	Color Index	Serum Iron, micrograms per 100 c.c
Normal	15.2 to 17.2	5.00+	46.5 to 51.1	1.0	99 to 158
Cancer of colon	4.4 to 13.6	2.40 to 5.89	27.5 to 42.1	1.0 to 0.5	22 to 76

not be determined. The transport fraction of blood iron should afford a much better estimate of the iron available for combating anemia.<sup>13</sup> Such determination made on the blood serum of patients with lesions of the proximal part of the colon proved most illuminating (fig. 153).

The values for iron in the serum of patients with right colonic lesions are shown in figure 153 and these values vary markedly from those of normal individuals. A summation of the blood findings in five normal individuals and in the twenty-one cases is given in table 1.

In cases in which the concentration of hemoglobin was high the concentration of serum iron frequently was low (fig. 153). The patient with low normal concentration of hemoglobin and slightly anemic blood findings had a maximal concentration of from 60 to 76 micrograms of iron per 100 c.c. and a minimal concentration of 30+ micrograms per 100 c.c. Even these maximal values were considered in the lower range of normal by Moore and his coworkers,<sup>14</sup> but are decidedly under the minimal values demonstrated in the five normal persons used for controls in this study.

The concentration of serum iron was definitely lower for the patients who had a moderate to severe anemia than it was in those with a low normal or slightly decreased concentration of hemoglobin. The concentration of iron varied from a minimum of 21.9 micrograms to a maximum of 48.3 micrograms per 100 c.c. of serum. These values for serum iron are as low as any noted in the literature on deficient iron metabolism and demonstrate a persistent decrease in this fraction so marked as not to be ignored.

The effects of iron therapy upon the concentration of serum iron and the blood as a whole furnish the final evidence that must be obtained to incriminate the iron metabolism as the element at fault in the production of the anemia under consideration. Such effects were observed (1) before operation, (2) after an exclusion procedure (ileocolostomy), and (3) following resection of the involved segment.

In only one case was the patient observed long enough before operation to permit the employment of adequate iron therapy. The concentration of serum iron could not be obtained in this case, therefore, it is not included in any subsequent part of this paper. When the patient presented himself for examination he was found to have a marked hypochromic, microcytic anemia accompanying a carcinoma of the ascending colon which had metastasized to the liver. The concentration of hemoglobin was 6.6 gm. per 100 c.c. of blood. The erythrocyte count was 3,450,000 and 1.5 per cent of the erythrocytes were reticulated. With no other therapy but 12 grains (0.73 gm.) of ferrous sulfate daily for seven weeks, the concentration of hemoglobin rose to a maximum of 11.4 gm. per 100 c.c. and the erythrocyte count increased to 4,650,000. The reticulocytes at the same time constituted 3.5 per cent of the erythrocytes.

Seven patients were observed following simple ileocolostomy. It was desirable to see just what effect exclusion of the lesion from the fecal current and relief of any incomplete obstruction that might be present would have upon the blood findings without iron therapy. Five patients therefore received no iron therapy and maintained approximately their status quo in the short interval of about three weeks before resection. One patient (case 5) was given iron orally and one patient (case 8) received liver and stomach concentrates. A comparison of these two patients receiving contrasting therapies affords an excellent insight into the problem. The patient who received iron therapy was able to maintain his concentration of hemoglobin and serum iron. The patient to whom the antianemic factor was administered became more anemic in a corresponding interval of two months. In both instances the cancer remained in situ and continued to bleed as demonstrated by repeatedly positive tests for occult blood in the stools.

Following resection of the involved segment of intestine, the rate of blood restitution with and without therapy was noted. The variation

TABLE 2—HEMATOLOGIC FINDINGS BEFORE AND AFTER RESECTION OF INTESTINE FOR CARCINOMA

Case	Specimen of Blood Obtained	Days	Hemoglobin gm per 100 c.c.	Erythrocytes millions per c.c.	Hematocrit Reading, per cent	Serum Iron, micrograms per 100 c.c.	Therapy
Two*	Before resection		12.6	4.76	41.7	39	12 grams of ferrous sulfate, daily for 20 days
	After resection	18	12.5	4.53	39.8	44	
	After resection	64	12.7	4.90	42.5	48	
Six	Before resection		11.8	4.86	38.9	56	Reduced iron 45 grams daily for 12 days
	After resection	12	12.3	4.44	42.6	35	
	After resection	26	12.2	4.40	39.0	44	
Ten	Before resection		10.5	4.10	35.7	32	Reduced iron, 30 grams daily for 5 days
	After resection	22	10.7	4.2	35.9	50	
	Before resection		9.7	4.52	35.9	30	Ferrous sulfate, 9 grams daily for 8 days
Eleven	After resection	13	9.9	4.0	39.1	31	
	After resection	27	11.6	3.8	36.5	92	
Fourteen*	Before resection		8.36	4.13	31.6	32	Ferrous sulfate 12 grams daily for 6 days
	After resection	17	10.4	4.52	39.3	46	
	After resection	38	11.1	4.85	43.1	53	
Nineteen	Before resection		6.6	4.26	36.6	36	Transfusion 500 c.c. of blood day of operation Reduced iron 30 grams daily for 9 days Ferrous sulfate 12 grams daily for 17 days
	After ileocolostomy	17	6.9	4.12	29.6	31	
	After resection	18	9.7	4.20	36.6	39	
Twenty-one*	After resection	40	13.4	4.60	48.9	94	Transfusion 500 c.c. of blood Reduced iron, 20 grams. Transfusion of total of 2000 c.c. of blood. Reduced iron 45 grams daily for 6 days
	Before resection	7	4.4	2.40			
	Before resection	6	7.9	3.0	26.3	120	
	After resection	16	12.7	4.42	43.3	88	

Four*	Before resection				4.35		39.8	45	
	After resection	24	13.4		4.46		46.0	98	
	After resection	40	15.7		4.56		48.1		
Seven	Before resection		11.2		4.46		36.0	35	
	After resection	7	9.2		4.01			40	
	After resection	32	11.56		4.23		36.8	61	
Eight	Before resection		11.2		4.39		37.0	32	Anemic factor Transfusion of blood 5 days after operation
	After ileocolostomy	115	8.6		4.3		30.6	36	
	After resection	17	9.5		4.06		33.8	35	
Twelve	Before resection		9.4		4.57		35.8	42	
	After ileocolostomy	48	9.6		4.5		36.0	80	
	After resection	23	10.0		4.2		29.6	29	
Twenty two†	Before resection		8.4		4.52		35.0	30	Transfusion of 500 c.c. of blood day of operation
	After resection	31	8.0		4.18		31.7	31	

Extraperitoneal resection performed.

† Carcinoma of rectosigmoid.

in the blood findings is recorded in table 2. The first seven patients received iron therapy, iron was withheld from the remaining five. Of the seven patients given medicinal iron the first three (table 2) exhibited only a moderate decrease in the initial concentration of hemoglobin and showed little change following resection and therapy. The remaining four, who had moderate to severe anemia, showed a decided response to oral administration of iron. Two of the latter patients (cases 11 and 19) are particularly interesting. Both received less than 1 gm of ferrous sulfate daily for eight and seventeen days, respectively, and demonstrated rapid progress toward normal hematologic findings. In the group of five patients who received no medicinal iron, the absorbed dietary iron must have been utilized in any regeneration of hemoglobin that occurred. The percentage of utilization of dietary iron is a factor that is influenced by many different conditions of the gastrointestinal tract.<sup>6, 8</sup> The variation in absorption and possibly in utilization of food iron is amply evidenced by these patients. The first two patients of this group showed absorption and utilization, as borne out by an improvement in the concentration of hemoglobin and an increase in the serum iron. The remaining three showed no evidence of absorption as the concentration of hemoglobin and serum iron remained unchanged.

In all cases, following resection of the cancerous segment of bowel, elevation of the hemoglobin values were accompanied by a return of the concentration of serum iron to a more nearly normal status regardless of the source, either dietary or medicinal, of the absorbed iron. The definite impression is obtained that iron therapy accelerates the recovery from the anemia, and that the more marked the hypochromic anemia, the greater the need for iron. The variable in this group of cases that continues to be confusing is that related to absorption, and this can possibly be eliminated only when a suitable preparation of iron for parenteral administration is available.

We have observed that patients with carcinoma of the left half of the colon who have an anemia (case 22) likewise demonstrate a lack of recovery from anemia if the concentration of serum iron shows no evidence of iron absorption.

In five cases resection was effected by the process of exteriorization and thus the colon was isolated from regions of absorption during the period of recovery from the anemia. As may be observed (table 2) this did not prevent the absorption of iron needed for elaboration of hemoglobin.

#### COMMENT

The concentration of hemoglobin was in the low normal range even in cases in which the highest concentration was obtained. Hypochromasia was the outstanding characteristic until the concentration of hemoglobin became very low. When this occurred the prevalence of microcytic erythrocytes in the circulation was increasingly observed. The color

index was below parity in all instances in which actual anemia was encountered, the more severe the anemia the less was the color index. Toxic destruction of the erythrocytes was not in evidence as they were generally not materially decreased in number and excessive regeneration was not present. The hypochromasia also increased and the color index decreased with the severity of the anemia. Such a condition does not obtain in the presence of excessive liberation of hemoglobin owing to abnormal destruction of erythrocytes by a hemolytic toxin. The toxin most likely to result from a lesion of this nature would be one elaborated by the cancer itself or by bacterial invasion of the ulcerated cancerous surface. Toxins from the presence of the cancer cells have not been demonstrated. In cancer, which is not associated with bleeding anemia rarely occurs until metastasis is present. As an example, in cases of nonulcerating cancer of the breast the value for the hemoglobin usually is normal.

It would not be expected that a cell which has reverted to its embryonal form would elaborate a highly specialized substance which would have a specific action in the destruction of blood. Also its function of absorption would be expected to be maternally deterred rather than enhanced by the lack of differentiation to adult form, as occurs in cancer cells. The presence of a cancer, if such a toxin were produced, would always result in anemia, which was not the finding in this study. The adjacent mucous membrane is in no wise changed by the presence of a nonobstructing carcinoma, therefore its likelihood of absorption of toxins can be assumed to be the same as that of a normal person. This leaves bacterial invasion of the cancerous growth and its effect upon the blood picture by its concomitant infection to be considered. Actually, in five of the twenty-one cases there was evidence of infection, as demonstrated by the polymorphonuclear leukocytes. The effect of infection upon the erythrocytes is spoken of as toxic suppression of the bone marrow function as related to hemapoiesis.<sup>17</sup> In such a condition not only the elaboration of hemoglobin is at fault but the maturation of the erythrocytes also is apparently delayed. This results in a decrease in both elements in the circulating blood. A normocytic anemia would be expected with anisocytosis, poikilocytosis and decided changes in the polymorphonuclear elements. Such is not the case in anemia associated with cancer of the right half of the colon as many of the patients who had severe anemia were entirely devoid of toxic manifestations. Even in two instances in which severe infection developed following operation there was no particular change in the degree or type of anemia. It is conceivable that a severe infection in a case of hypochromic anemia could increase the anemia by increasing the demands already being exerted on the hemapoietic system, by rendering the patient so ill as to prevent proper ingestion of food or medicinal iron and by retarding the formation of hemoglobin along with a general depression of metabolic activities.



If the anemia that occurs with a cancer situated in the right colon is not due to absorption of toxin, could it conversely be the result of a decreased absorption of an antianemic element from the diseased segment of bowel? It has been demonstrated that the right half of the colon or even the whole colon can be excluded from absorption and the individual recover from the anemia. Therefore, malabsorption from this portion of the bowel would not be evinced by the production of an anemia.

What effect could cancer of the right half of the colon exert on the formation of hemoglobin to render it deficient when cancer in the distal segment of colon rarely exerts a similar influence? It could cause an excess demand for hemoglobin by long continued chronic hemorrhage. It has been demonstrated that the largest and most friable malignancy of the entire gastro-intestinal tract can and does exist in the proximal part of the colon for a long time without producing obstruction or other severe symptoms.<sup>1</sup> To lose blood means the loss of iron, and since the dietary iron absorbed at one time is very small,<sup>8, 10</sup> the iron lost by hemorrhage from such a growth could readily exceed the daily intake of iron in the food. If such should continue for many months it may readily be seen that the iron reserves available for the formation of hemoglobin would be depleted and a subnormal condition of the blood supervene. Although the lesions in the left half of the colon bleed frequently, the bleeding is from a small tumor and is readily discovered, as the red blood may be expelled unmixed with feces. Lesions of the left half of the colon rarely had existed for anything like the duration of the lesions of the right half of the colon without producing an obstruction. When an anemia does occur in association with carcinoma of the distal portion of the colon it is a hemoglobin deficiency anemia and is in no wise different from the anemia observed in cases of carcinoma of the right half of the colon.

With abnormal loss of iron through chronic hemorrhage there is an increased demand for it, of course.<sup>23</sup> This demand can be met by the stored iron only so long as it is not depleted. If hemorrhage continues the absorbed, ingested iron must be adequate or hypochromic anemia will occur.<sup>7, 10</sup> Is it possible for a carcinoma situated in the proximal part of the colon to exert an effect upon the absorption of iron from the intestinal tract, and if so, is this effect more pronounced than that exerted by lesions in the distal portions of the colon? It appears from the comparative study of the symptoms produced by cancer in the proximal and in the distal portions of the colon that just such a situation occurs. The principal symptoms of cancer of the right half of the colon, other than anemia, are indigestion and diarrhea. The indigestion is apparently reflex as the association of disturbances in the cecum and ascending colon and referred epigastric pain and discomfort is notorious. Nausea and vomiting, gaseous distention, epigastric pain, anorexia,

and preprandial and postprandial discomfort are all encountered characteristically in cases of carcinoma of the right half of the colon. Such symptoms greatly limit the intake of food and the tendency is to eat light foods which have little value as a provider of dietary iron. In cases of cancer of the distal portion of the colon the symptoms are usually local, and until obstruction has occurred deficient intake of food is not likely to be a factor.

Other factors influencing the absorption of iron from the gastrointestinal tract are more in evidence in cases of carcinoma of the right half of the colon than in cases of carcinoma of the left half of the colon. In eighteen of the twenty-one cases of cancer of the right half of the colon analysis of the gastric contents was made, no free hydrochloric acid was present in eight of these cases and in several of the cases an excess of mucus was present in the gastric contents. It has been demonstrated<sup>2, 4, 9</sup> that both of these factors can cause a deficient absorption of dietary iron.

#### SUMMARY

The type of anemia that occurs with cancer of the proximal portion of the colon has been observed to be the same as that produced by a deficient supply of iron for elaboration of hemoglobin. The abnormal demands made upon the iron supply of the body have been noted to be increased in instances in which the growth is situated in the proximal segment, while the ingestion and absorption of dietary iron appeared to be more retarded than they were when the growth was situated in the distal portion of the colon. The presence of other associated deleterious factors influencing absorption has been surmised. Study of the concentration of serum iron has furnished additional confirmation that a deficiency of iron is present. In all cases of cancer of the right half of the colon the concentration of serum iron was low. If severe anemia was present, a very marked decrease in the concentration of serum iron was observed. The anemia could apparently be arrested, with the cancer in situ, following iron therapy if the iron was of sufficient amount and was absorbed. Recovery from the anemia following removal of the cancer was demonstrated to be dependent upon adequate absorption of iron. Administration and absorption of iron following resection of the involved segment of colon resulted in a return of a normal concentration of serum iron and hemoglobin. Anemia accompanying carcinoma of the distal portion of the colon has been observed in two instances to be similar to that observed in conjunction with carcinoma of the proximal portion of the colon.

#### REFERENCES

1. Alvarez, W. C., Judd, E. S., MacCarty, W. C. and Zimmermann, A. R., The varying degrees of anemia produced by carcinoma in different parts of the colon. *Arch. Surg.* 15:402-417 (Sept.) 1927.
2. Barer, Adelaide P. and Fowler, W. M., Influence of gastric acidity and degree of anemia on iron retention. *Arch. Int. Med.* 59:785-792 (May) 1937.

- 3 Broders, A. C The grading of carcinoma *Minnesota Med.* 8 726-730 (Dec) 1925
- 4 DAVIES, D T Studies on achlorhydria and anaemia. *Quart. J Med* 24 447-467 (July) 1931
- 5 Deaver, J B Surgery of the right half of the colon *Ann Surg* 80 439-449 (Sept.) 1924
- 6 Hahn, P F Metabolism of iron *Medicine* 16 249-266 (Sept.) 1937
- 7 Hahn, P F and Whipple, G H Iron metabolism, its absorption, storage and utilization in experimental anemia *Am J M Sc* 191 24-42 (Jan) 1936
- 8 Heath, C W and Patek, A J., Jr Anemia of iron deficiency *Medicine* 16 267-350 (Sept) 1937
- 9 Heath, C W, Minot, G R, Pohle, F J and Alsted, Gunnar The influence of mucin upon the absorption of iron in hypochromic anemia. *Am J M. Sc* 195 281-286 (Mar) 1938
- 10 Josephs, H W Studies on iron metabolism and influence of copper *J Biol Chem* 96 559-571 (May) 1932
- 11 Keefer, C S Anemia associated with gastrointestinal disorders clinical considerations and the value of iron in treatment *Ann Int. Med* 5 740-749 (Dec) 1931
- 12 Keefer, C S, Yang, C S and Huang, K K Anemia associated with chronic dysentery clinical considerations, with special reference to the cause and treatment *Arch Int. Med* 47 436-466 (Mar) 1931
- 13 Moore, C V, Doan, C A and Arrowsmith, W R Studies in iron transportation and metabolism II The mechanism of iron transportation its significance in iron utilization in anemic states of varied etiology *J Clin Investigation* 16 627-648 (July) 1937
- 14 Moore, C V, Arrowsmith, W R., Quilligan, J J and Read, J T Studies in iron transportation and metabolism I Chemical methods and normal values for plasma iron and "easily split-off" blood iron. *J Clin Investigation* 15 613-626 (July) 1937
- 15 Prickman, L E The changes in the blood picture with carcinoma of the colon *Proc Staff Meet, Mayo Clin* 2 80-82 (Apr 13) 1927
- 16 Rankin, F W, Bargaen, J A and Buie, L A The colon, rectum and anus. Philadelphia, W B Saunders Company, 1932, p 472
- 17 Robschert-Robbins, F S and Whipple, G H Infection and intoxication their influence upon hemoglobin production in experimental anemia *J Exper Med* 63 767-787 (May 1) 1936
- 18 Sanford, A H and Sheard, Charles The determination of hemoglobin with the photo-electrometer *J Lab & Clin Med* 15 483-489 (Feb) 1930
- 19 Sherman, H C Chemistry of food and nutrition Ed 5, New York, The Macmillan Company, 1937, 640 pp
- 20 Todd, J C and Sanford, A H Clinical diagnosis by laboratory methods A working manual of clinical pathology Ed 8, Philadelphia, W B Saunders Company, 1935, 792 pp
- 21 Van Slyke, D D and Neill, J M The determination of gases in blood and other solutions by vacuum extraction and manometric measurement *J Biol Chem* 61 523-573 (Sept) 1924
- 22 Welch, C S, Mayo, C W and Wakefield, E G A histological study of the intestine proximal to carcinoma of the right side of the colon, associated with anemia *Surgery* 2 419-430 (May) 1935
- 23 Whipple, G H and Robschert-Robbins, F S Blood regeneration in severe anemia III Iron reaction favorable—arsenic and germanium dioxide almost inert *Am J Physiol* 72 419-430 (May) 1925

## TESTS OF LIVER FUNCTION

JAMES F WEIR

THE diagnosis and management of diseases of the liver and biliary tract fundamentally rest on the evaluation of clinical data. The procedures have been established through long periods of clinical practice and have been reasonably satisfactory. There are certain instances in which a clinical diagnosis cannot be made with certainty. In some such cases, the patients have been denied the possible benefits of surgical exploration, in other cases surgical procedures have been employed to the detriment of the patient, particularly if parenchymatous disease of the liver has been present. During the past two or three decades, much new knowledge concerning the physiology of the liver has been developed and, as a corollary of this attempts have been made to determine the nature, extent and significance of functional abnormalities in various types of disease of the liver or biliary tract. This has led to the development and use of many tests of liver function. In the use of such tests, attempts have been made to apply them to the differential diagnosis and management of such diseases with, unfortunately, an unwarranted halo of importance and significance. Actually these tests are somewhat limited in value yet no apologies are needed for their judicious employment.

Such tests presuppose a knowledge of the functions of the liver and there are many of these. Approximately thirty-three different, though related, functions of the liver cells have been listed and it is estimated that at least 100 chemical activities are known to occur in the liver. In view of this, the following question may be asked, "What is a liver function test?" One answer, elementary and facetious, might be, "Some laboratory procedure that reveals something wrong with the liver." That something is wrong is usually known before employment of the procedure, from clinical observation, such as enlargement of the liver, jaundice or ascites. This answer may be satisfactory in cases in which clinical evidence of disease is absent. Perhaps a better answer would be, "A procedure that shows a disturbance, and perhaps the degree of such disturbance, in some particular function of the liver." Obviously in view of the many functions of the liver, its known large reserve and great regenerative capacity, no "miracle" test can be expected, that is, no single test can be anticipated that will determine deviations from normal of even a few major functions of the organ, let alone all of them.

Some authors claim that the chief value of these tests is the detection of early functional disturbance or focal disease such as carcinoma or abscess. Because of the known large reserve capacity, severe and ex-

tensive damage is necessary before positive tests may be obtained in such conditions. Consequently, some physicians would say that the tests lack sensitivity. Others claim that the tests are too sensitive. Positive results may be obtained but no clinical signs of disease of the liver may be apparent or develop. Rafsky, and Newman, for example, have reported a considerable group of aged persons on whom positive tests were obtained in the absence of clinical evidence of disease of the liver. The question may then be asked, "Is a positive test an indication of disease of the liver or only of a dysfunction (as diarrhea in a case of irritable colon), and if it is an indication of dysfunction what is its significance?" Answer to this question is difficult to give. The significance of minor deviations from normal are particularly difficult to evaluate. The results must always be interpreted in association with other available data. In some instances, the findings are significant, in others, correlation of the findings is impossible.

If tests are to be used clinically, they must be readily performed, reliable, and give some worth-while information from a diagnostic, therapeutic or prognostic standpoint. In addition, the results must be capable of being interpreted easily. Probably about seventy-five to 100 tests for liver function have been devised. The large number of these that have been used and discarded is evidence of their failure to meet the criteria which I have mentioned. The multitude of tests and the claims and counterclaims made in regard to them have created a very confusing situation, particularly for the general practitioner. It would seem well, therefore, to consider a few of the more simple procedures and their practical application.

In such a consideration, certain facts should be pointed out. First, diagnostic procedures should be distinguished from tests for liver function, thus, duodenal drainage and examination of the stools for bile are best classified as diagnostic procedures because they are primarily used to determine the patency of the bile ducts. Such procedures leave much to be desired.

Second, there are two groups of cases in which tests of liver function are commonly used (1) cases of suspected liver disease in which jaundice is absent, and (2) cases of jaundice. In the first group, the dye excretion tests and van den Bergh test are particularly valuable. In the second group, it is necessary to determine whether the jaundice is hemolytic, obstructive or hepatogenous. Hemolytic jaundice is usually readily distinguished by clinical and hematologic studies, and the van den Bergh test is also helpful. The last two types of jaundice usually are distinguished by clinical study, chiefly by the history in regard to pain or exposure to infection and hepatotoxins, by physical evidence of abdominal tumors, and by employment of diagnostic procedures to determine the patency of bile ducts. Some aid in this distinction may be obtained from the use of some of the tests of liver function, such as the distribution of urobilinogen in the urine and feces, the van den

Bergh test, the galactose tolerance test and the partition of cholesterol in the plasma

Thus, then, is the first practical use of tests of liver function, that is, assistance in the differential diagnosis of various types of jaundice. Their second use is for the confirmation of the presence of liver damage in cases in which it is suspected and the evaluation of the extent of liver damage in cases in which the presence of disease of the liver or biliary tract is known. The qualitative and quantitative determination of serum bilirubin by the van den Bergh test, dye excretion tests, hippuric acid synthesis, galactose tolerance test, blood prothrombin time, partition of cholesterol in the blood and the value for the protein in the blood are procedures most commonly used in the study of such conditions but they give information of variable value. Many of these are not truly functional tests but laboratory procedures which throw some light on one or another aspect of disease of the liver. In the interpretation of the results of such tests in the presence of jaundice, it should be remembered that there is seldom any case of jaundice pure in type. For example, severe hepatic damage may occur in cases of obstruction of the biliary tract or in hemolytic processes, and the tests may be valuable in these types of disease as well as in primary parenchymatous disease of the liver.

Third, and finally, there is the question of progression of activity of disease of the liver or recovery. Repetition of some of these tests aids in the determination of this point. Some physicians claim that the cephalin-cholesterol flocculation test is of particular value as such an indicator.

Some of these tests will now be considered individually and in more detail. The first of these is the *van den Bergh test*, which is used to determine the type and quantity of bilirubin in the serum. It also can be applied to the duodenal contents and urine. Various modifications of the original test have been developed.<sup>1</sup> Prior to two years ago, we employed the technic of Thannhauser and Andersen but since then the technic of Sepulveda and Osterberg has been used. This permits the quantitative determination separately of the indirect and direct reacting bilirubin in the serum in any given case. In health, the value for the bilirubin is less than 0.6 mg. per 100 c.c. of serum and it reacts indirectly with Ehrlich's diazo reagent. In pathologic states such as pernicious anemia, congenital hemolytic icterus, other hemolytic conditions and familial hyperbilirubinemia, the reaction is characteristically indirect. In these conditions the concentration of the bilirubin in the serum usually is variably increased. In many cases of cirrhosis, metastatic tumors of the liver and other pathologic conditions of the liver without evident jaundice, the reaction to the van den Bergh test may be indirect. This type of reaction does not exclude any of these pathologic processes. Pigmentation, such as that due to carotene and atabrine, must be distinguished from icterus. In cases in which pig-

mentation is due to carotene or atabrine, the concentration of serum bilirubin is normal and the reaction is indirect. A direct reaction always is a pathologic finding and is commonly encountered in the various forms of obstructive and hepatogenous jaundice. Such a reaction also is present in the latent jaundice at times seen after biliary colic, in acute cholecystitis, in metastatic tumors of the liver and in many cases of chronic and even acute hepatitis. In the presence of a hemolytic process, a direct reaction indicates an associated hepatic or biliary disorder. Little attention from a clinical standpoint need be given to biphasic or delayed direct reactions.

The quantitative determination shows the degree of retention of bilirubin and its fluctuations from time to time. In many instances estimations every few days are necessary to determine whether the jaundice is stationary, increasing or decreasing in severity. In obstructive jaundice due to stone in the common bile duct, the average value for the serum bilirubin is 10 to 15 mg per 100 c c. Fluctuations frequently occur and there is a general tendency for the bilirubinemia to decrease. In neoplastic obstruction of the common bile duct, average values are higher, that is 20 to 30 mg per 100 c c. Fluctuations seldom occur and the jaundice is persistent. In parenchymatous disease of the liver, the degree of icterus is variable. In some cases, very mild degrees of bilirubinemia are encountered. On the other hand, some of the highest concentrations (70 to 100 mg per 100 c c) encountered are due to this type of disease of the liver. The higher concentrations are indicative of more serious disorganization of the liver. In obstructive jaundice, similarly high concentrations (that is, much above the average concentration) are indicative of an associated hepatic degeneration.

The *icterus index* is a simple and approximate method of following the degree and variations of bilirubinemia in any case of icterus and is used in many laboratories.

*Dye excretion tests* are frequently used in the determination of liver function. Various dyes may be used, such as phenoltetrachlorophthalein, tetraiodophenolphthalein, Bengal red and bromsulfalein. These tests depend on the rate of disappearance of the dye from the blood stream. It has been our custom at the Clinic to use bromsulfalein. We inject 5 mg of the dye per kilogram of body weight of the patient, remove a specimen of blood in one hour and determine the amount of dye remaining in the blood with a block colorimeter. Normally, little remains in the blood at the end of one hour. The presence of 40 per cent or more indicates a high degree of retention. Various modifications of this technic have been made but I doubt their practical importance. This is one of the best tests of liver function in cases in which jaundice is not present. The presence of jaundice is a contraindication to the use of this test. When jaundice is present, the test merely shows the impairment to be expected, as indicated by retention of bilirubin and furnishes no additional information. The test is to be used in cases

in which disease of the liver is suspected when jaundice is absent. These diseases include enlargement of the liver and spleen, suspected metastatic tumor or abscess, ascites and toxic hepatitis such as may occur in cases of exophthalmic goiter, toxemias of pregnancy, many infections, poisoning with various therapeutic and industrial chemicals and many other conditions. Normal values usually are obtained in abdominal enlargement due to ovarian cysts, peritoneal carcinomatosis and tuberculous peritonitis. In cardiac disease with decompensation and chronic passive congestion, a moderate to high degree of retention of the dye usually is encountered. Ascites due to portal obstruction from canalized portal thrombosis usually gives normal values but some disturbance of excretion of the dye occasionally is found. In cases of suspected metastatic tumors or abscess of the liver, and occasionally in cirrhosis the values may be normal. In cases of splenomegaly in which splenectomy is being considered, high degrees of retention may be encountered, indicating a high surgical risk and a poor prognosis. In some cases in which the patients are in reasonably good health mild degrees of retention of the dye occasionally are encountered but no definite disease of the liver can be demonstrated and no satisfactory cause for the retention can be found. In some instances, dehydration and starvation may be etiologic factors. In other instances, these are absent but in spite of lack of any explanation, the findings are probably of some significance.

The *hippuric acid test* depends on the ability of the liver to furnish glycine to permit the synthesis of hippuric acid from benzoic acid (administered as sodium benzoate). It is claimed to be a test of the detoxicating function of the liver. The presence of disease of the kidney should be excluded before this test is employed. The amount of hippuric acid excreted in the urine is determined gravimetrically. After administration of 6 gm of sodium benzoate, at least 2.5 to 3 gm as hippuric acid should appear in the urine in four hours. Less than 1.5 gm. is indicative of impairment of liver function. The test does not aid in distinguishing obstructive jaundice from hepatogenous jaundice. In cases in which jaundice is absent, the results parallel those obtained with the bromsulfalein test. An intravenous method of performing the test has been devised and is employed by many physicians.

The *galactose tolerance test* is one of the sugar tolerance tests used to determine deviations of the normal function of the liver to metabolize carbohydrates. Galactose is chiefly utilized by the liver, and in the performance of the test it may be administered orally or intravenously. When the galactose is administered intravenously, the test is spoken of as the "galactose clearance test." In using the test it is necessary that the presence of diabetes mellitus be excluded. If oral administration is employed, 40 gm of galactose in 500 c c of water is given and the urine is collected over a five hour period and examined for sugar. Normally, less than 3 gm of sugar should be excreted. Excretion of more than 5 gm



is indicative of severe hepatic damage. In acute hepatitis, positive tests may be obtained early (less than two weeks). In obstructive jaundice, the test may become positive at the end of two weeks. In our experience at the Clinic, the test has been found mildly positive in 50 per cent of cases of malignant obstruction and in 25 per cent of cases of obstruction due to stone or cicatricial stricture. Normal results do not exclude the possibility of parenchymatous origin of jaundice.

The *prothrombin time* should be determined in all cases of jaundice, particularly if the disease is surgical, in which case it should be determined during the preoperative and postoperative periods. In the laboratories of the Clinic, the method of Quick, as modified by Magath,<sup>2</sup> is used. With this method, the normal values are eighteen to twenty seconds. Elevation of the prothrombin time may be due to deficient intake, deficient absorption or deficient utilization of vitamin K. Deficiency of intake is seldom a factor in jaundiced conditions. A deficiency of absorption is common in the acholia of jaundice. It also occurs in intestinal disorders such as those associated with sprue. Deficiency of utilization of vitamin K is encountered chiefly in parenchymatous disease of the liver. In this disease, the vitamin K is not converted into prothrombin, and if the damage to the liver is severe, administration of vitamin K will not control the hypoprothrombinemia and its associated hemorrhagic manifestations. The degree of this failure is an indication of hepatic insufficiency. Data accumulated in the past two years indicate that larger doses than formerly employed may be advisable when small doses are ineffective. Vitamin K should be administered in all cases of jaundice, whether or not the prothrombin time is prolonged. This is particularly true in cases in which operation is to be performed and the administration should be continued during the postoperative period.

Another test is the determination of the distribution of *urobilinogen* in the feces and urine. Much of the recent work in this field has been done by Watson and by Steigmann and Dyniewicz.<sup>5, 6</sup> The methods are tedious and complicated but Watson has simplified the procedure to a great extent. Normally, much of the bilirubin of bile entering the intestine is changed to urobilinogen. Much of this is absorbed into the blood stream, passes to the liver and is reconverted to bilirubin. Under normal conditions, 30 to 200 mg of urobilinogen is excreted in the feces during twenty-four hours. Small amounts appear in the urine (0.2 to 3 mg in twenty-four hours). Persistent absence of urobilinogen from the feces (and urine) indicates that bile is not entering the intestine, and hence complete obstruction of the biliary passages. This is most frequently seen in cases of malignant tumors but occasionally occurs from a stone impacted in the common bile duct and from complete cicatricial stricture of the bile ducts. A marked increase in urobilinogen in the feces (up to 3,600 mg in twenty-four hours) is

encountered in the various hemolytic processes such as congenital hemolytic icterus and pernicious anemia. In diseases of the liver, such as acute hepatitis and active cirrhotic processes, the normal conversion of absorbed urobilinogen to bilirubin is interfered with and excessive amounts of urobilinogen appear in the urine. In such diseases, there is frequently a decreased amount of bilirubin entering the intestine and, consequently, less urobilinogen can be formed. Nevertheless, increased urinary urobilinogen is the usual finding. In inactive cirrhosis without jaundice, variable amounts of urobilinogen are found in the feces and urine. In these circumstances, interpretation of the results should be made with caution. Summarizing, one may say that the presence of the substance in the feces indicates that the bile passages are not occluded and that excessive amounts in the urine indicate some impairment of liver function or the presence of an associated hemolytic process.

Determination of the concentration of several of the constituents of the blood often gives valuable information on sufficiency or insufficiency of some of the functions of the liver. The *protein content of the serum* normally is from 6 to 8 gm per 100 c.c. In chronic parenchymatous disease of the liver and at times in the latter stages of acute parenchymatous disease, the concentration of the proteins of the blood is reduced. This is particularly true of the albumin fraction, thus reversing the albumin-globulin ratio. The value for the globulin may be increased. The decrease in concentration of the albumin apparently is due to failure of its fabrication by the liver rather than to deficiency of intake or absorption or an abnormal loss. The hypo-albuminemia produces a lowered colloid osmotic pressure of the blood and is a factor in the formation of edema and ascites, which frequently are encountered in chronic disease of the liver. Although hypo-albuminemia is frequently encountered in disease of the liver, there are many instances, particularly those in which the condition is of short or moderate duration, in which normal values for protein do exist and, in rare instances, an increased concentration of protein may be noted.

Abnormalities of the partition of *fats in the plasma* are at times encountered in various types of jaundice. However, little is known of the significance of many of these changes. In general, there is a mild to moderate increase in all the fats of the plasma in obstructive jaundice. This is particularly true of cholesterol and cholesterol esters. The concentration of these two components may be decreased in acute parenchymatous disease of the liver and the ester fraction may be entirely absent. Such absence or a marked decrease of this fraction has been used as a prognostic sign, and often indicates a fatal outcome. Marked increase in the concentration of all of the plasma lipids occurs in certain rare chronic diseases of the liver, such as xanthomatous biliary cirrhosis as well as in other chronic metabolic disorders, such as xanthoma tuberosum. In considering these changes in plasma lipids,

is necessary that the presence of these metabolic diseases, as well as that of diabetes mellitus and nephrosis be excluded Hypolipemia is also encountered in sprue and certain rare diseases of the pancreas

Elevation of the concentration of *blood urea* may occur if involvement of the kidneys develops in the course of disease of the biliary tract or liver Occasionally, a lowering of the concentration of blood urea occurs in cases in which long-standing and chronic disease of the liver is approaching its terminal stage Lowering of the concentration of *blood sugar* and associated hypoglycemic symptoms occasionally may be found in cases of chronic disease of the liver in the absence of any demonstrable pancreatic disorder The concentration of *serum calcium* may be lowered in chronic obstructive jaundice, such as that due to cicatricial stenosis of the common bile duct This apparently is due to deficiency of absorption of calcium caused by the acholia Osteoporosis and spontaneous fractures (particularly of the vertebrae) are usually accompaniments The concentration of *plasma chlorides* and the *carbon dioxide combining power of the plasma* are altered in cases of external biliary fistula especially if the fistula is complete or nearly complete, and in cases in which cholestasis is present. Dehydration, hypochloremia, acidosis with their accompanying symptoms ensue

Several *serologic tests* based on alterations of the blood proteins, particularly the globulin fraction, have been developed These include the Takata-Ara, the colloidal gold, and Hanger's cephalin-cholesterol flocculation tests Only the last-mentioned test has any support at present It has been advocated as a means of distinguishing obstructive jaundice from parenchymatous jaundice but these claims have not been substantiated There is some evidence that it may be of some value in the estimation of the activity of hepatic disease

The laboratory procedures and tests of liver function that I have mentioned are the ones that we have commonly employed at the Clinic in the past few years It is still our firm conviction that the diagnosis and management of diseases of the biliary tract and liver are largely based on clinical grounds and that the results of the various tests are rather limited in value The tests do not distinguish obstructive jaundice from hepatogenous jaundice although they may furnish some assistance in such distinction. They do not distinguish acute disease of the liver from the chronic type They do not indicate the cause of cellular disintegration However, some estimate of functional capacity of the liver in several respects can be made from data afforded by several of the tests, particularly with their judicious repetition They afford some aid in following the clinical course of disease of the liver, in determining the risk of surgical procedures, in directing preoperative and postoperative treatment and nonsurgical treatment, and in evaluating the prognosis Although these tests have limitations, the data obtained are usually significant. Interpretation of results may be difficult, especially if deviations from normal are slight Positive

tests are much more significant than negative ones. Negative results do not necessarily exclude the existence of disease of the liver or disturbances of hepatic function. Furthermore in some cases, it seems impossible to correlate all the findings adequately. In such cases, particularly, clinical data should be followed and at a later date the tests may be repeated. Finally, the tests do have a value in teaching the physiology of the liver and in research.

## REFERENCES

1. Magath, T. B. The serum bilirubin test. (Editorial) *J Lab & Clin Med* 18: 974-980 (June) 1933
2. Magath, T. B. Technique of the prothrombin time determination. *Am J Clin Path.* (Tech. Suppl.) 3: 187-189 (Sept.) 1939
3. Rafsky, H. A. and Newman, Bernard. Liver function tests in the aged. (The serum cholesterol partition, bromsulphalein cephalin flocculation and oral and intravenous hippuric acid tests.) *Am J Digest. Dis.* 10: 66-69 (Feb.) 1943
4. Sepulveda, B. and Osterberg, A. E. Serum bilirubin. Its clinical importance and a recommended procedure for the determination of indirect and direct values. *Proc. Staff Meet., Mayo Clin* 18: 252-258 (July 28) 1943
5. Steigmann, Frederick and Dymiewicz, Josephine M. Studies of urobilinogen. I. The daily urobilinogen excretion in urine and feces in health and disease: an evaluation of Watson's and Sparkman's methods. *Gastroenterology* 17: 743-764 (Aug.) 1943
6. Steigmann, Frederick and Dymiewicz, Josephine M. Studies of urobilinogen. II. Quantitative urobilinogen determinations in the differential diagnosis of jaundice. *Gastroenterology* 17: 855-875 (Sept.) 1943
7. Thannhauser, J. S. and Andersen, E. Methodik der quantitativen Bilirubinbestimmung im menschlichen Serum über die Ehrlich-Pröschersche Reaktion. *Deutsches Arch. f. klin. Med.* 137: 179-186, 1921
8. Watson, C. J. Studies of urobilinogen. I. An improved method for the quantitative estimation of urobilinogen in urine and feces. *Am J Clin Path.* 6: 438-475 (Sept.) 1936

# CONSTITUTIONAL HEPATIC DYSFUNCTION

MANDRED W COMFORT

FROM time to time, cases of mild acholuric jaundice, in which hemolytic, hepatic or biliary tract disease is suspected as the cause, are encountered. The abdomen occasionally has been opened without finding disease of the biliary tract or of the liver, and splenectomy, cholecystectomy, cholecystostomy or even choledochostomy has been performed without relief of the jaundice. Medical measures that are used in treatment of hepatic disease likewise have not relieved the jaundice. More recently, jaundice of this type has been the cause for contemplated dismissal of men from the armed forces of our country.

Actually the jaundice in these cases is not due to disease of the blood, liver or biliary tract but apparently is due to an abnormally high threshold for excretion of bilirubin formed at the usual rate. The concentration in the serum reaches 10 to 12 mg per 100 c c, and the van den Bergh reaction is indirect. The jaundice is acholuric in type since bilirubin that gives the indirect van den Bergh reaction is not excreted by the kidneys. It is presumably due to an inborn deficiency of the hepatic cells especially with respect to the excretion of bilirubin. The terms "simple familial cholemia," "simple chronic icterus," "familial cholemia" and "familial nonhemolytic jaundice" have been applied to the condition<sup>7-10, 15</sup> but at the Clinic we prefer to call it "constitutional hepatic dysfunction" because this term indicates the constitutional nature of the condition as well as the organ now believed to be responsible.

The jaundice may not be noted before examination or may have been apparent continuously or intermittently for years. It may begin at any age and often several members of a family are affected similarly. The patient may be extremely healthy and vigorous but he frequently complains of lack of endurance and symptoms of the functional type. He may give a history suggestive of cholecystic disease, with or without stones. Physical examination usually does not disclose abnormalities other than a slight icteric tint to the scleras. The liver and spleen are not enlarged and, as mentioned previously, the urine is free from bile pigment (acholuria). The level of serum bilirubin is increased and the van den Bergh reaction is indirect. The results of morphologic examination of the cellular elements of the blood are normal, as is the fragility of the erythrocytes to hypotonic salt solution. The excretion of urobilinogen in feces for twenty-four hours is said to be normal or slightly decreased.<sup>5</sup> Other tests of hepatic function have not disclosed dysfunction of the polygonal cells other than that related to excretion of bilirubin. Although roentgenograms of the gallbladder made by the Graham-Cole technic usually disclose normal function, they may dis-

close a poorly functioning or nonfunctioning organ with or without stones. However, this incidental finding cannot be held responsible for the increased level of serum bilirubin giving the indirect van den Bergh reaction.

### HISTORICAL MATERIAL

The jaundice of constitutional hepatic dysfunction has been recognized since 1902, when the first of a series of articles by Gilbert and his associates appeared. They called attention to a group of cases in which the bile pigment in the blood was greater than normal. This finding was not associated with enlargement of the liver or spleen. Icterus of the skin and scleras often was apparent. Bile pigments did not appear in the urine. While Gilbert and associates<sup>7-10</sup> probably included among their cases patients who had hepatic and hemolytic disease, particularly chronic hemolytic icterus and even carotinemia, they deserve credit for recognition of a familial type of acholuric jaundice unassociated with enlargement of the liver and spleen.

Subsequent refinements of diagnosis permitted differentiation of the various disease processes that produce an increased concentration of serum bilirubin giving an indirect van den Bergh reaction but little attention was given to the jaundice of constitutional hepatic dysfunction. In 1935, Rozendaal, Snell and I<sup>2, 13</sup> reported the first large series of cases of constitutional hepatic dysfunction. This condition was encountered sixty times at the Clinic during a two year period. In 30 per cent of the sixty cases, cholecytic disease was present. This high percentage suggested that constitutional hepatic dysfunction predisposed to the development of cholecytic disease but the high incidence may have been the result of the method of selection of cases and the greater frequency with which the concentration of serum bilirubin is determined in cases of cholecytic disease than in other cases.

Meulengraecht in 1939,<sup>12</sup> Dameshek and Singer in 1941<sup>8</sup> and Curry, Greenwalt and Tat in 1942<sup>4</sup> discussed the condition and reported cases. Curry and associates described biopsy in the case of a man, fifty years of age, who had constitutional hepatic dysfunction. The hepatic structure and cells were normal. It is interesting that a similar jaundice exists among a certain strain of rats, as reported by Malloy and Lowenstein.<sup>11</sup>

In 1944, Hoyne and I<sup>3</sup> reported a series of thirty-five cases collected from the records of the Clinic over an eight year period since the report in 1935. In case 3 of that report features of chronic hemolytic icterus of the acquired type developed. The spleen became palpable and the erythrocytes became microcytic. The fragility of the erythrocytes increased in the four year interval between the first and second examinations. In other cases of constitutional hepatic dysfunction, microcytosis but not spherical microcytosis has been observed. These findings raise the question of relationship between constitutional hepatic dysfunction and chronic hemolytic icterus, that is whether hepatic

dysfunction of the type seen in constitutional hepatic dysfunction exists in chronic hemolytic icterus

### INCIDENCE

The true incidence of the disease among patients who register at the Clinic probably is much nearer the average of thirty per year, as reported in 1935, than the average of four per year, as reported in 1944. The incidence in the latter report would have been greater if the records had been examined of all cases in which the concentration of serum bilirubin with an indirect van den Bergh reaction was greater than 2 mg per 100 c c, this was done in preparing the 1935 report.

### DIFFERENTIAL DIAGNOSIS

The recognition of constitutional hepatic dysfunction as a distinct clinical entity is important, not because it affects the health of the individual but because a correct diagnosis avoids the erroneously serious prognosis of true hepatic disease, prolonged medical treatment and unnecessary surgical treatment. The diagnosis would be made more often if all abnormally high elevations of serum bilirubin with an indirect reaction were examined more critically and if the concentration of bilirubin and the indirect or direct nature of the van den Bergh reaction were determined whenever the patient complains of slight jaundice, biliousness, liverishness and sallowness.

The diagnosis of constitutional hepatic dysfunction should be made only after the presence of hemolytic and hepatic disease has been eliminated.

Hemolytic disease is excluded by the absence of history of exposure to toxic, infectious and parasitic agents with hemolytic properties, by the absence of anemia and splenomegaly and by normal morphologic examination of erythrocytes, normal fragility of erythrocytes to hypotonic salt solution and normal excretion of urobilinogen in the urine and feces. Occasionally splenomegaly occurs in a case that otherwise conforms to the definition of constitutional hepatic dysfunction but the latter diagnosis should not be made without further observation and study because of the possibility of atypical hemolytic icterus.

Most types of jaundice due to hepatic disease are excluded at once by the indirect nature of the van den Bergh reaction. The various hepatic functional tests further serve to exclude other dysfunction of the hepatic cells and, inferentially, disease of the hepatic cells. Only when the serum bilirubin responsible for latent jaundice of hepatic disease gives the indirect van den Bergh reaction is a differential diagnosis necessary. Slight latent jaundice due to serum bilirubin giving the indirect van den Bergh reaction often precedes the jaundice of hepatic disease with its more characteristic direct van den Bergh reaction, and may persist for months and even years after recovery from profound damage to the hepatic polygonal cells and after other

hepatic functional tests have become negative. In such cases the history of hepatic damage serves to point to the nature of the disturbance to which the term residual hepatic dysfunction may be applied.

In an occasional case of constitutional hepatic dysfunction the retention of dye in the bromsulfalein test of hepatic function has been increased to 6 or 7 per cent at the end of one hour (normal retention 5 per cent), but in no case has the percentage been increased more than might be accounted for by the human factor. Similarly, the van den Bergh reaction occasionally has been delayed direct instead of indirect, just as it is in the occasional case of true hemolytic icterus but this has occurred only when the concentration of bilirubin was relatively high. When the new technic of Sepulveda and Osterberg<sup>14</sup> has been used in such cases the serum bilirubin has been of the indirect variety. The rate of excretion of bilirubin in congenital hepatic dysfunction is said to be decreased, as is to be expected from the nature of the process.

The jaundice that results from hepatitis associated with cholecystic disease or from obstruction of the duct due to stone is attributable to an increase in the concentration of bilirubin giving a direct van den Bergh reaction. It is accompanied by other characteristic features of disease of the biliary tract, especially colic, and should not be confused with the jaundice of constitutional hepatic dysfunction.

### THREE ILLUSTRATIVE CASES

The following abstracts of cases, previously included in the 1944 report by Hoyne and me, illustrate the typical features of constitutional hepatic dysfunction. Jaundice was the sole manifestation of the condition. Disease of the blood, liver, spleen or biliary tract could not be demonstrated.

CASE 1.—A man, aged sixty years, registered at the Clinic in September 1938. He was a highly successful, energetic person who had more than the usual amount of endurance. His sole complaint was recurrent attacks of jaundice associated with fatigue, which he thought were precipitated by worry, nervous stresses, anger and constipation. The jaundice was painless and was not associated with chills, fever, nausea or vomiting. The stools remained normal in color during the attacks. There were no general or abdominal symptoms between attacks. The last two episodes of jaundice had followed renal colic. These attacks had occurred since early life and long had been of concern to both the patient and his physicians. The last attack had occurred several months before registration. His mother, one sister and a niece had experienced similar episodes of jaundice.

The results of general physical examination were negative with the exception of an icteric tinge to the scleras and skin. The liver and spleen were not palpable. Urinalysis and routine serologic test for syphilis gave negative results. The hemoglobin was 14.8 gm per 100 c.c. of blood, erythrocytes numbered 4,790,000 and leukocytes 7,000 per cubic millimeter of blood. Morphologic study of the blood did not disclose abnormality of the cells. Fragility of the erythrocytes to hypotonic salt solution was normal. Roentgenograms of the thorax, gallbladder, esophagus and stomach and bromsulfalein and hippuric acid tests for hepatic function



gave negative results. The concentrations of serum bilirubin were 3.0 and 1.6 mg per 100 c.c. and the van den Bergh reaction was indirect.

The diagnosis was constitutional hepatic dysfunction. The patient recently reported by letter that the episodes of icterus still occurred two or three times a year but that otherwise he had been getting along well.

*Comment*—The jaundice in case 1 was familial. It was chronic and latent most of the time but overt at intervals when its depth was increased by nervous and emotional factors. Although the attacks had occurred for forty years, they apparently had not affected the patient's health or diminished his endurance, and had not led to the development of disease of the blood, liver, spleen or biliary tract. This case emphasizes the effect of nervous and emotional stress on the depth of the jaundice, an effect that long has been recognized<sup>1, 5, 6, 12</sup>. The jaundice that occurs after renal colic must be explained on a similar basis.

**CASE 2**—A man, aged thirty-five years, registered at the Clinic in June, 1938. Except for thyroidectomy in 1930 and appendectomy and tonsillectomy in 1937, his health had been good. His endurance was satisfactory and fatigue occurred only after long periods of intense work. About six months prior to registration the patient had had a short period of malaise with slight jaundice and some loss of weight. The jaundice had persisted after the malaise disappeared and had fluctuated in intensity. Several doctors had diagnosed the condition as acute hepatitis or catarrhal jaundice. A high carbohydrate diet and various medicines including calcium, vitamin B and dilute hydrochloric acid had been prescribed.

The results of general physical examination were essentially negative with the exception of slight scleral icterus. Urinalysis and routine serologic test for syphilis gave negative results. The hemoglobin was 15 gm per 100 c.c., erythrocytes numbered 4,900,000 and leukocytes 8,100 in each cubic millimeter of blood. The erythrocytes were normal in size and shape. Fragility of the erythrocytes to hypotonic salt solution was normal. Gastric analysis after a test meal showed free acidity. Roentgenograms of the thorax, gallbladder and stomach were negative. The basal metabolic rate was -3 per cent. The concentration of serum bilirubin was 2.0 mg per 100 c.c. and the van den Bergh reaction was indirect. Brom-sulfalein test of liver function did not disclose retention of dye.

The diagnosis was constitutional hepatic dysfunction.

The patient was not aware that other members of his family were similarly affected but on inquiry on his return home he found that his brother had a more yellowish tinge to his eyes than the patient. He also learned that his father's family was noted for the yellowish tinge to their complexions, some members of the family having this to a marked degree. His maternal antecedents were fair skinned and there was no history of jaundice among them.

*Comment*—Case 2 again illustrates that constitutional hepatic dysfunction is compatible with excellent endurance and health. The jaundice was discovered when the patient was thirty-five years of age, and then only because his physician was a careful examiner. Concern about the jaundice was only natural and treatment for hepatitis was without benefit. The patient's anxiety was dispelled when the nature of the condition was explained and only on inquiry was the familial incidence of the condition established.

**CASE 3**—A woman, aged forty years, registered at the Clinic in December, 1934. Ill health developed in 1919 at the age of twenty five years. There was fatigue, nervousness, insomnia and epigastric distress which appeared soon after, or as long as one hour after, meals and then shifted to the lower portion of the abdomen. The discomfort was accompanied by marked bloating and pressure in the left upper quadrant of the abdomen, palpitation of the heart and dizziness. Vomiting occurred at the time of leaving the table or soon afterward. Constipation with the passage of large amounts of mucus was a prominent feature of her problem. The whites of the eyes became yellow with the more severe attacks of nervousness, fatigue and abdominal distress and usually also when she was badly constipated. Other members of the family did not exhibit jaundice.

Vigorous efforts had been made to cure the patient. In addition to various medical measures, appendectomy had been performed in 1919. The jaundice had aroused suspicion of the biliary tract, consequently cholecystectomy had been performed in February, 1933, and exploratory choledochostomy and gastro-enterostomy in October, 1933. Tonsillectomy later was undertaken. All surgical procedures, as well as medical measures, had failed to influence the severity of her complaints or the jaundice.

On examination at the Clinic, urinalysis and serologic test for syphilis gave negative results. The hemoglobin was 17.4 gm. per 100 c.c., erythrocytes numbered 4,360,000 and leukocytes 8,300 per cubic millimeter of blood. The results of differential count of leukocytes were normal. The reticulocytes numbered 0.7 per cent. Morphologic study of the blood did not disclose abnormal cells. Fragility of the erythrocytes to hypotonic salt solution was normal. Analysis of the gastric contents after a test meal showed small amounts of free acid. Roentgenograms of the thorax and colon were normal. Those of the stomach showed the gastro-enterostomy to be free and the stomach to be normal. The duodenum was not visualized. The concentration of serum bilirubin on two occasions was 2.7 and 3.7 mg. per 100 c.c., with an indirect van den Bergh reaction. The bromsulphalein test of hepatic function did not disclose retention of dye.

The diagnosis was chronic nervous exhaustion, mucous colitis and constitutional hepatic dysfunction.

In a recent letter the patient stated that the scleral icterus still appeared whenever she became markedly fatigued and after spells of severe abdominal distress. A bland anticonstipation diet and an improved program of living had produced improvement.

**Comment**—The patient in this case complained, as do so many patients who have constitutional hepatic dysfunction, of a multitude of symptoms of the functional type. The jaundice was intensified and became overt under stimulation of increased fatigue and emotional and nervous stress but scarcely could be blamed for the patient's disability. The attacks of jaundice continued in spite of the institution of numerous medical and surgical procedures. The jaundice was not familial which is true in certain cases of constitutional hepatic dysfunction.

#### PROGNOSIS

The general health of the patient who has constitutional hepatic dysfunction may remain excellent. Some patients may have no complaints and may be curious only about the jaundice (cases 1 and 2). In most cases the patient may, and probably does, have other complaints.

since otherwise he would not consult a physician. Such complaints are usually functional but may be of some other type. It is not certain that the fatigue and lack of vitality so frequently complained of are due to the condition.

As previously mentioned, the liver was normal in the one case in which biopsy has been performed.

### TREATMENT

Whether treatment of constitutional hepatic dysfunction is indicated is questionable since it apparently does not affect the general health. Treatment such as is given in disease of the liver is disappointing and is not indicated. Cholecystectomy, choledochostomy and splenectomy have no influence on the course of the jaundice or on the functional complaints of the patient. Operations on the biliary tract are indicated only when bona fide disease of the gallbladder or calculous disease of gallbladder or ducts exists. Avoidance of preceipitating stresses such as overwork, fatigue and emotional and nervous stress may lessen the depth and the frequency with which increases in depth of jaundice occur.

### COMMENT AND SUMMARY

Attention is again called to constitutional hepatic dysfunction, a condition in which jaundice is due to an inborn inadequacy of the hepatic cells, particularly with regard to excretion of bilirubin. Its sole clinical manifestation is acholuric jaundice. The jaundice may be latent or overt. The essential pathologic finding is an increase in serum bilirubin giving an indirect van den Bergh reaction. It is not due to hemolytic or true hepatic disease or disease of the biliary tract. The prognosis is excellent. Its recognition is important to prevent an erroneously serious prognosis and unwarranted medical and surgical treatment.

### REFERENCES

- 1 Chrometzka, Friedrich. Über die Norm des Bilirubinspiegels des Menschen und die hyperbilirubinämie, I Mitteilung zur Kritik der quantitativen Bilirubinbestimmung im Serum des gesunden und kranken Menschen. *Ztschr f d ges exper Med* 67 475-481, 1929.
- 2 Comfort, M W. Constitutional hepatic dysfunction. *Proc Staff Meet., Mayo Clin* 10 57-61 (Jan 23) 1935.
- 3 Comfort, M W and Hoyne, R M. Constitutional hepatic dysfunction: clinical study of thirty-five cases. *Gastroenterology* 3 155-162 (Sept) 1944.
- 4 Curry, J J, Greenwalt, T J and Tat, R J. Familial nonhemolytic jaundice, report of a case with liver biopsy. *New England J Med* 226 909-912 (June 4) 1942.
- 5 Dameshek, William and Singer, Karl. Familial nonhemolytic jaundice, constitutional hepatic dysfunction with indirect van den Bergh reaction. *Arch Int Med* 67 259-285 (Feb) 1941.
- 6 Eppinger, Hans and Hess, Leo. Vagotonia, a clinical study in vegetative neurology. In *Nervous and Mental Disease Monograph Series No 20* (Trans-

lated by W M Kraus and S E Jelliffe) New York, The Nervous and Mental Disease Publishing Company 1915 93 pp

- 7 Gilbert, A and Lereboullet, P La cholemie simple familiale. *Gaz. hebdomadaire de med* 49:889-897 1902
- 8 Gilbert, A. and Lereboullet P Sur la teneur en bilirubine du serum sanguin dans la cholemie simple familiale. *Compt. rend. Soc. de biol.* 58:937-940 (June 3) 1905
- 9 Gilbert, A. and Lereboullet, P La cholemie simple familiale son importance en pathologie. *J med franc.* 4:110-119 1910
10. Gilbert A., Lereboullet, P and Herscher M Les trois choleemies congenitales. *Bull et mem. Soc med d hop de Paris.* 24:1203-1211 (Nov 15) 1907
11. Malloy, Helga T and Lowenstein, Louis Hereditary jaundice in the rat *Canad. M A J* 42:122-125 (Feb) 1940
12. Meulengracht, L. Icterus intermittens juvenilis (Chronischer intermittierender juveniler Subikterus) *Klin Wchnschr* 18:118-121 (Jan 28) 1939
- 13 Rozendaal, H M., Comfort, M W and Snell A M Slight and latent jaundice the significance of elevated concentrations of bilirubin giving an indirect van den Bergh reaction *J.A.M.A* 104:374-379 (Feb 2) 1935
- 14 Sepulveda, Bernardo and Osterberg A E. Serum bilirubin a procedure for the determination of indirect and direct values *J Lab & Clin Med* 28:1359-1368 (Aug) 1943
- 15 Tecon, R M Les hyperbilirubinemies hereditaires la cholemie familiale et l'ictere hemolytique. *Arch d mal de l'app digestif* 28:567-589 (June) 1938.

# DIFFERENTIAL DIAGNOSIS OF NEPHRITIS

MELVIN W BINGER

THE disease commonly known as glomerulonephritis presents many varied and interesting problems in etiology, differential diagnosis and treatment, and it is the purpose of this paper to consider some of these problems

The disease, as first described by Richard Bright in 1827, was but vaguely understood and even now, more than one hundred years later, there are many aspects of the disease that are largely a matter of conjecture.

The disease presumably is due to an inflammation or toxic reaction of the capillary loops of the glomeruli, which is really an endocapillaritis and an involvement of a part of the vascular system. In the acute form it very frequently is associated with or follows infections of the upper part of the respiratory tract, tonsillitis, scarlet fever and other infectious processes. It has been determined by various investigators, and from our records at the Clinic, that in about 85 per cent of cases of acute glomerulonephritis the disease is attributable to infectious processes. It is hard to conceive that the organism causing the primary respiratory or other infection is transmitted by the blood and lodged in the kidneys, thus producing the glomerular changes. It is thought rather that toxins from the primary infection are the causative factor. The possibility of a virus exists and many investigators have considered an allergic reaction as the cause of the glomerular changes.

However, it is not my purpose to go into minute detail regarding the etiology and pathology and treatment of glomerulonephritis, but rather to consider the differential diagnosis of glomerulonephritis and suggest some of the common pitfalls in the diagnosis of this disease.

To make a diagnosis of glomerulonephritis solely on the presence of albumin and blood and casts in the urine is a hazardous procedure and may result in the wrong diagnosis, for many other disorders in the body may produce abnormal urinary findings.

*Polycystic kidneys* will produce the identical clinical picture of chronic glomerulonephritis and the differential diagnosis frequently is not easy, especially in cases in which the patients are obese and the concentration of blood urea is increased. The obesity makes palpation of the kidneys difficult and, if the value for the blood urea is more than 70 or 80 mg per 100 c c, intravenous urography is not a satisfactory method for outlining the kidneys as the iodine compound is not sufficiently concentrated to be visualized on the urogram. Retrograde pyelograms can be made, but always with some hazard. However, the size of the kidneys frequently can be outlined on the roentgenogram. If the value for the blood urea is normal or nearly normal,

excretory urography offers the best procedure for diagnosis. The outline of the distorted calices is quite typical in cases of polycystic kidney.

There may be a familial history of polycystic kidney which will give a lead for investigation. The course is more benign as a rule than that of chronic glomerular nephritis, and a high concentration of blood urea is better tolerated. The blood pressure will be elevated as in chronic glomerulonephritis with the usual diffuse vascular disease. Renitis develops as the disease progresses and cardiac degeneration and decompensation are common.

*Chronic pyelonephritis* is often mistaken for chronic glomerulonephritis, in the chronic, latent phase it may closely resemble the latter disease. In chronic pyelonephritis there is usually a history of recurrent infection of the urinary tract, with fever and chills, pyuria and often hematuria and bacteria usually *Escherichia coli* frequently are found in the urine while bacteriuria is rarely seen in chronic glomerulonephritis. Intravenous urography usually will disclose distortion of the calices and pelvis of the kidneys owing to inflammatory changes. Often there is an associated cystitis which can be detected by cystoscopic examination. Stones often can be demonstrated in one or both kidneys and frequently will take the characteristics and form of pelvis and calices, forming the so-called staghorn stones. The infection may involve one or both kidneys. As the disease progresses there results a gradual renal impairment with all the characteristics of chronic glomerulonephritis namely, hypertension, uremia, vascular and cardiac changes and anemia.

If the disease is limited to one kidney the clinical picture will be the same, except that the remaining kidney will usually carry on the necessary excretion of nitrogenous matter unless or until resultant hypertension and vascular changes impair its function. If unilateral atrophic pyelonephritis is detected early and if the involved kidney is removed surgically the blood pressure may be restored to normal and the systemic progress of the disease may be checked. However if the disease has progressed sufficiently to cause serious vascular damage and serious impairment of the other kidney through vascular changes the results of removal of a unilateral atrophic kidney are not so spectacular and will do little or no good. Again, in this instance, intravenous urography, retrograde pyelography and selective functional studies of the kidneys are important. The incidence of unilateral atrophic kidney resulting from chronic pyelonephritis is so common in cases of hypertension that the neurosurgeons insist on having excretory urograms made to rule out the presence of this condition before considering a splanchnic resection for the hypertension. I personally do not think that splanchnic resection should be considered in any case of hypertension until satisfactory intravenous urograms are made and unilateral or bilateral atrophic pyelonephritis has been definitely excluded as an etiologic factor. In fact, excretory urography is being

recognized more and more as an important diagnostic aid in cases of hypertension and chronic glomerulonephritis, to be sure that one is not dealing with atrophic pyelonephritis. I know of no situation that gives me more satisfaction than to find, and have removed, an atrophic kidney in a case in which the patient seemed doomed and, by this surgical procedure, restore a patient to health.

A condition that somewhat resembles atrophic pyelonephritis is *congenital hypoplastic or malformed kidney*, which may or may not produce hypertension and diffuse vascular changes. If hypertension is detected in a child, urologic studies should be made to rule out the presence of a unilateral hypoplastic kidney. If such a kidney is found, its removal should be seriously considered. This condition can and will produce the clinical picture of malignant hypertension.

*Tuberculosis of the kidneys* or of a single kidney may be confused with chronic glomerulonephritis, and, when pus and blood, as well as albumin, persistently occur in the urine, a centrifuged specimen of urine should be stained for *Mycobacterium tuberculosis*. If any doubt exists about the presence of this organism, guinea pigs should be inoculated. Excretory urography and cystoscopy are of immense diagnostic help. Fortunately, tuberculosis usually affects only one kidney and, if the involved kidney is removed, the chance of recovery is good. At present, chemotherapy does not seem to be of much value in this disease.

*Hypernephroma of the kidney* may produce albumin and blood in the urine. Usually, there are recurrences of gross blood in the urine. The malignant lesion may be far advanced before there is any clinical indication of its presence and I have seen cases of widespread metastasis in which the primary source was found by urologic studies. If the hypernephroma is discovered and nephrectomy done early, and if deep roentgen therapy is employed subsequently, the immediate outlook is favorable.

*Adenomyosarcoma*, or Wilms' tumor, in children may present the clinical picture of hypertension and nephritis. However, it is rarely encountered and the outlook is invariably poor. Urologic studies should be carried out in cases in which the presence of this tumor is suspected.

In the advanced stages of *essential hypertension* it is quite difficult or impossible to tell by the findings alone whether the primary condition was glomerulonephritis or essential hypertension. The albuminuria and sediment in the urine are similar in each disease. The impairment in renal function, the anemia, and the degree of hypertension are confusingly alike in the two diseases, and the end results, such as uremia, cardiac failure or cerebral vascular accident, occur with about equal frequency in the two diseases. In many instances, only the pathologist who examines the renal tissue can in any measure be certain as to which was the primary disease. However, there are certain

points in the history and physical examination that lend a clue. In chronic glomerulonephritis, there is often a history of acute nephritis which occurred after an infection of the upper part of the respiratory tract or other infection associated with fever. The acute glomerulonephritis is associated with edema, oliguria and gross hematuria. Early in the disease, the vascular changes and hypertension are less in evidence and the urinary abnormalities are more dominant. Albuminuric or vascular retinitis may or may not be present, and spasm and narrowing of the retinal arteries may be noted. In essential hypertension, the onset, course and symptoms may vary in intensity and character and the disease may not produce symptoms or may not be detected until it is well advanced. In many cases the disease is detected first at an insurance examination. Army medical examinations disclose many instances of essential hypertension in which the men were previously unaware of the disease. Nervousness, headache, insomnia, irritability, easy fatigability, dyspnea on exertion and, later failing vision, hematuria and albuminuria will be found. The retinas will usually show more sclerosis and retinitis than is seen in chronic glomerulonephritis. However in many cases of chronic glomerulonephritis the onset may be insidious and the disease may be far advanced and extensive secondary diffuse vascular disease may be present before the patient is aware that anything is wrong. It is in such cases in which the history is indefinite and the onset is insidious, that the differential diagnosis is difficult, and it is surprising how frequently one encounters this problem. However at this stage, the problem becomes chiefly academic and the treatment, course and prognosis are about the same in both diseases and from all practical aspects the two diseases become one and the same disease.

*Subacute bacterial endocarditis* can and frequently does present a clinical picture not unlike that of chronic glomerulonephritis and must be suspected in cases in which albuminuria and hematuria are present, particularly if there is evidence of mitral or aortic valvular disease or congenital cardiac anomaly such as patent intraventricular septal defect, patent ductus arteriosus, patent foramen ovale or coarctation of the aorta. Blood cultures should be made in suspected cases and if *Streptococcus viridans* is found, together with the cardiac findings, fever, petechia and general debility it is quite safe to presume that the renal findings are secondary to the primary infection in the blood stream. Space will not permit a detailed consideration of subacute bacterial endocarditis itself. In most cases the disease is due to *Streptococcus viridans* infection of a damaged heart valve, usually the mitral, or of congenital heart lesions. It is probable that the urinary picture is produced by emboli lodging in the glomeruli of the kidneys, resulting in abscess formation and destruction of renal substance. Hypertension is unusual in cases of subacute bacterial endocarditis and, when it is present, one must suspect pre existing vascular disease of ess



hypertension, chronic glomerulonephritis, or other diseases that produce hypertensive vascular disease. It is not common to see uremia in cases of uncomplicated subacute bacterial endocarditis. It is fairly common to see cases of subacute bacterial endocarditis in which repeated blood cultures are negative, and one should not be misled by negative blood cultures.

*Periarteritis nodosum* or diffuse endarteritis produces a myriad of symptoms and clinical findings that may be confused with those of chronic glomerulonephritis. There may be albumin, casts and erythrocytes in the urine, and hypertension and evidence of widespread cardiovascular disease. However, the severity and rapid progression of the clinical symptoms and findings are out of proportion to what one would expect in cases of chronic glomerulonephritis. Usually, the retinal findings are minimal and the evidence of cardiac damage is much more profound in periarteritis nodosum than it usually is in chronic glomerulonephritis. There, too, will usually be peripheral neuritis and pain and soreness in muscles and tenderness along certain arteries, which do not occur in cases of nephritis. If painful nodules along the arteries can be found, the evidence is rather in favor of periarteritis nodosum. A biopsy of a suspected nodule or region will frequently be the deciding clue in the diagnosis. Unfortunately, this disease presents such a widespread and atypical clinical picture that it usually goes unrecognized before death and, more frequently than not, the diagnosis is finally established by the pathologist at necropsy. The legion of clinical findings, the unusually rapid progress of the disease, the widespread organic involvement, the usual leukocytosis, fever, severe cardiac failure and cerebral involvement without definite clinical syndromes should lead one to suspect the presence of periarteritis nodosum.

*Acute disseminated lupus erythematosus* in many ways resembles periarteritis nodosum and subacute bacterial endocarditis and will produce a clinical picture that is easily confused with that of glomerulonephritis. It is thought by some investigators to be a closely related disease as far as the cause, clinical findings and course are concerned. It runs a subacute course with fever, progressive anemia and pronounced leukopenia. There may be pericarditis, arthritis and an erythematous and purpuric rash, usually involving the face but frequently also the extremities. Blood cultures are invariably negative. The protean nature of the clinical picture is thought by some investigators to be due to the widespread vascular involvement.

In advanced *pulmonary tuberculosis* and tuberculous involvement of other organs, the urinary findings, such as albuminuria, casts and hematuria, may be mistaken for those of chronic glomerulonephritis. These findings may result from the toxic effect on the kidneys or from tuberculous lesions of the kidneys. In the latter instance, *Mycobacterium tuberculosis* may be found in the urine. A widespread

amyloidosis may be present and can be readily detected by the Paunz test. Usually, careful general clinical studies including roentgenologic examination of the thorax, will be of help in establishing the correct diagnosis. There usually will not be the vascular involvement and hypertension that generally are seen in cases of chronic glomerulonephritis.

However in considering *amyloidosis* as a cause of albuminuria, it must be remembered that tuberculosis, although the most common, is not the only predisposing cause. There are cases of widespread amyloidosis in which a definite cause cannot be determined and because of the accompanying albuminuria, hypoproteinemia and edema the disease may be mistaken for a nephrotic stage of chronic glomerulonephritis. The downhill course of widespread amyloidosis, however, is much more progressively rapid than is nephrosis, which is relatively a mild disease, in comparison, and will run a fatal course in a few weeks or months. There will be evidence of severe damage of the liver with marked retention of dye, edema, ascites, usually of a chylous nature and rapidly failing renal function. The Paunz test will be strongly positive.

Amyloidosis also may be observed in many cases of large tumors, particularly those involving the bones and in syphilis, in multiple myeloma and in some cases of leukemia. In cases of atypical and rapidly declining nephrosis the Congo red test or the Paunz test should be done to be sure that one is not confronted with this disease.

In most cases of *multiple myeloma*, there is an unusual type of albuminuria which is known as Bence-Jones albuminuria, and, in cases of albuminuria, a test should be made for this type of protein. The test is quite simple and the result is characteristic. A white precipitate is formed when nitric acid is added to the urine, this precipitate disappears on boiling and reappears on cooling. In suspected cases, roentgenograms of the ribs, long bones and skull should be made to demonstrate whether the peculiar multiple lesions of bone are present. Frequently, sternal aspiration of bone marrow for microscopic study will reveal the myelomatous cells.

Bence-Jones protein however does not occur only in cases of multiple myeloma but may be found in some cases of leukemia, chloroma, myxedema, chondrosarcoma and malignant tumors of the gastrointestinal tract. In contrast to chronic glomerulonephritis and nephrosis, the serum proteins are usually elevated.

A rather rare disease that might at first consideration be confused with chronic glomerulonephritis is *hyperparathyroidism* due to adenoma of the parathyroid glands. Albuminuria, uremia, anemia and even hypertension may be observed. However, in about two-thirds of the cases there will be typical bone changes of osteoporosis and cystic degeneration of the bones. In some cases the disease may be confused with multiple myeloma. In most cases the value for the serum calcium

will be more than 11 mg per 100 c c and the value for the inorganic serum phosphorus will be less than 3 mg per 100 c c It is probable that in many of these cases the disease escapes diagnosis and is considered as nephritis or other systemic disease

In further consideration of the condition commonly known as *chronic lipid nephrosis*, one is confronted by the two schools of thought as to whether lipid nephrosis is a variety of chronic glomerulonephritis, or whether it is a degenerative disease of the kidneys and not a manifestation of chronic glomerulonephritis In my observations of cases of so-called lipid nephrosis, the disease eventually has progressed to typical chronic glomerulonephritis with uremia, hypertension and diffuse cardiovascular involvement Cases in which severe albuminuria, hypoproteinemia, and edema, hyperlipemia with normal or only moderately elevated blood pressure, and a normal concentration of blood urea are considered as chronic glomerulonephritis with the nephrotic syndrome The nephrotic syndrome apparently occurs in cases in which the nephritis is benign and in which so much albumin is lost through the urine over a long period of time that the concentration of serum protein is depleted to or below the critical level of 5 per cent, which results in a lowering of the colloidal osmotic pressure and of the blood, resulting in edema It is not clearly understood why there should be an increased permeability of the glomerular loops, conceding, of course, that the filtration of plasma proteins takes place through this element of the kidneys Neither is it clear why some patients with the nephrotic syndrome will have a normal blood pressure while others will have severe hypertension and vascular involvement It is thought to be due to the degree of impairment or unimpairment of blood flow through the kidney, which has been ably demonstrated by Goldblatt and other investigators

Lipemia is not peculiar to nephrosis alone, for it is frequently observed in cases of proved chronic glomerulonephritis

In *Hodgkin's disease* and *lymphosarcoma*, the clinical picture of nephritis is frequently observed There may be albumin, casts and erythrocytes in the urine, as well as renal failure, as evidenced by an increased concentration of blood urea Blood pressure may also be elevated and anemia may be present However, the generalized adenopathy, enlarged spleen and frequently the typical mediastinal widening are clues favoring the diagnosis of these diseases Frequently occurring attacks of fever of the Pels-Ebstein type may be noted Biopsy of a lymph node is advisable and frequently will establish the diagnosis It is thought the renal changes are due to infiltration of the kidneys by the malignant process However, in some cases only toxic changes were noted on microscopic studies Marked improvement is frequently noted after roentgen therapy Blood counts and smears are helpful in distinguishing Hodgkin's disease and lymphosarcoma from chronic leukemia, and the microscopic appearance of the

lymph nodes is typical of either disease. Usually splenomegaly is much more pronounced in leukemia than in lymphosarcoma and the spleen may attain an enormous size.

Whenever pus and blood are present in the urine, together with albumin, and particularly when the sediment is stringy and clotted, it is well to investigate the urethra, bladder and kidneys for some gross urologic lesion and not assume unequivocally that the patient has nephritis. Excretory urography and cystoscopic examination can easily disclose inflammatory lesions vesical stones, cystitis, ureteral and renal stones, vesical tumors, diverticuli of the bladder enlarged prostate with obstruction, secondary infection of the urinary tract and many other conditions that, on the basis of the urinalysis alone, would simulate nephritis.

In conclusion, I would say that the errors in diagnosis of renal disease and of any diseases which secondarily affect the renal system and produce abnormal urinary findings are made in assuming that the cause of the abnormal urinary findings is nephritis rather than keeping an open mind and considering other possibilities. Merely because most cases of albuminuria with microscopic hematuria, and casts together with hypertension and anemia are cases of nephritis does not indicate by any means that they all are. It is only by a careful analysis of the history physical examination and laboratory findings that one can hope to eliminate errors in diagnosis.

The importance of intravenous urography, cystoscopic and other urologic studies in cases of suspected nephritis should be emphasized.

## CHRONIC CERVICITIS

MONTÉ C PIPER

CHRONIC cervicitis may include erosion of various types and degrees, chronic cellulitis and fibrosis, cysts, polyps, lacerations with infection, eversion and malignant changes

Symptoms resulting from chronic cervical involvement may be purely local or more extensively systemic. There is individual variation in the degree of distress. Rather extensive involvement of the cervix may produce surprisingly little discomfort in some cases and the diagnosis may be determined only by examination. In others the involvement may be mild but may seem to produce symptoms of an unwarranted severity.

Leukorrhea usually accompanies any degree of chronic cervicitis and is the most frequent finding. Pelvic weight or heaviness is often aggravated by fatigue and, if the paracervical ligaments are much involved, may result in actual pain. Dyspareunia may be complained of. Menstrual irregularities or abnormalities and increased dysmenorrhea sometimes accompany chronic involvement. Metrorrhagia should lead to careful search for any possible early malignant process. Sterility is sometimes corrected by eliminating cervical lesions.

More remote symptoms are most frequently complained of as urinary distress. The close proximity of the ureters and base of the bladder to the network of lymphatics, vessels and nerves surrounding the cervix explains the frequency of urinary complication. Both infections and neoplastic processes may readily invade the region of the bladder and the ureters by direct extension.

The history of a patient who has chronic cervicitis may be clarified by a frequent review of the salient points. Frankly discussing with the patient her ideas about her symptoms and explaining to her the findings and their probable significance will help to encourage her confidence and to manifest the physician's understanding of, and sympathy with her in, her problem. Some women hesitate to tell their story completely at first and it may happen that the patient will divulge her innermost fear only after treatments are completed and at the time of dismissal. Her chief anxieties may be summed up in the fear of having some loathsome disease, of development of a malignant lesion or of an inability to perform her normal sexual functions. The history should record duration, remissions and previous therapeutic attempts.

Pelvic heaviness or pain usually is responsive to the application of heat, to rest and to some of the more common analgesics. Back pain in the sacrolumbar region often accompanies cervicitis and its relief may follow elimination of the cervical involvement. It is fairly frequent for a patient to state that a chronic backache has been relieved in a

very few days after a cauterization of chronic cervical fibrosis containing multiple cysts

Records of about 1,000<sup>5</sup> cases in which cervical cauterization had been performed from six to nine years previously were reviewed and questionnaires sent to the patients. Four hundred and forty had listed backache in their histories as one of their complaints. Of the patients who answered the questionnaire, 62 per cent reported the backache relieved while an additional 11 per cent said that the backache had been improved. It was not assumed that the treatment of the cervix was the only factor contributing to their relief but such a record seems significant.

The assumption that chronic cervicitis is a focus of infection in more remote regions is probably more speculative than proved but streptococci are often found on culture taken from cervical lesions. Some ocular conditions, such as episcleritis, have responded favorably after correction of cervicitis and in cases of infectious rheumatism the cervix should be examined as a possible source.<sup>1</sup> Certain types of renal infection seem likewise to lose their tendency to exacerbations after the chronic cervical involvement has been healed. Some authors have classed the cervix as being as important as the tonsils and teeth as a source of infective processes.

Chronic cervicitis is most frequently inaugurated at childbirth and thus occurs in the third or fourth decade of life, which is perhaps the age of greatest stress and strain to the mother. The psychic effect on her personality when she is relieved of her nagging pelvic distress is gratifying.

The etiologic production of cervicitis is commonly attributed to infection though there are cases of erosion of the cervix in which it is difficult to discover an infection as a preceding involvement.

Infective processes are usually superimposed on some form of trauma such as that produced during childbirth with the bruising and lacerations, in some previous instrumentation or as the result of an acute infection overwhelming the defense mechanisms. There is a resulting residue in the endocervical glands and tissues of the portio vaginalis and adjacent structures. The chronic infective organism is usually a streptococcus but its invasion may have been made possible by an acute onslaught in which organisms such as *Neisseria gonorrhoeae*, *Escherichia coli*, some types of staphylococci, diphtheroids, *Mycobacterium tuberculosis* and other less common bacteria were producers of the initial acute process. The foregoing acute infection may have destroyed the defense barriers of the tissues and that may have allowed the invasion of the streptococci. Racial and environmental characteristics may vary the incidence of the less frequent organisms but the streptococcus seems to be the offender which persists after the primary acute inflammation has subsided.

A rather violent epithelial irritation may be set in action by parasitic

organisms such as *Trichomonas vaginalis*, *Monilia albicans* and some others and thus prepare a means by which streptococci gain access to deeper tissue and institute a more extensive involvement than is usually observed in cases of parasitic vaginitis. It is not known that the foregoing parasites of the vagina have invasive properties in themselves but it is believed that they act in symbiosis with pathogenic bacteria and allow of deeper chronic involvement.

Defensive processes against infection in the cervix are manifested by an intricate anatomic structure of the endocervix and by the outflow of alkaline mucus, which is then liquefied and acidified in the vaginal vault by the action of the vaginal fluids. A mild chemical reaction thus occurs about the portio vaginalis. This process varies in different individuals and is influenced by their degree of natural immunity and general condition of bodily health. It is further varied by the hormonal influence on the vaginal epithelium in the quantity of glycogen available for conversion into lactic acid in the vagina, by the outflow of menstrual fluids and no doubt by other influences such as psychic stimuli not well understood.

Examination of the patient in anticipation of treatment for any condition is benefited by a general systemic review. A good physical examination is as essential in dealing with pelvic conditions as in dealing with conditions in any other portion of the body. Leukorrhea being the most frequent symptom of cervicitis, the nature of the discharge should be sought and its origin ascertained. Cultures and smears are advisable to determine the presence of *Neisseria gonorrhoeae*, *Trichomonas vaginalis* or *Monilia albicans* and the character of the pus and of the desquamated epithelial cells. There are likely to be a suggestive odor and consistency to secretions associated with the foregoing types of infection and gonorrheal infection is likely to reveal involvement of Bartholin's and Skene's glands. Malignant processes have an odor of necrotic tissue and secretions may be watery and blood stained.

Palpation should acquaint the examiner with the tone of the tissues of the vagina and supportive ligaments and the position, size and consistency of the cervix, the fundus and the adnexae. Nabothian cysts may possibly be more readily palpated than visualized. Palpation through the rectum is advisable if possible, as the adjacent cervical tissues and uterosacral and broad ligaments are often more accurately palpable by rectal than by vaginal examination.

Inspection of the cervix requires that the patient be in a comfortable position. If the vagina is unduly sensitive, a mild local anesthetic may be used. A good light is essential. Evidences of lacerations, edema, polyps, erosions, cysts, bleeding points and ulcerations are looked for. A small cold light introduced into the cervical canal may reveal by translucence deeply buried cysts which would otherwise be unsuspected. Gently pressing on the surface of the portio vaginalis with a blunt tipped probe may reveal irregularities of resistance and spongy

regions from which one may desire to remove tissue for biopsy. Perhaps tissue should be removed for biopsy from all lesions of the cervix but certainly from papillary or polypoid regions regions which tend to bleed after slight trauma, an obvious ulcer, areas of leukoplakia or areas which are velvety and allow the probe to sink readily into the substance of tissue, a specimen should be removed and examined by a pathologist. A diffuse milky gray color of the surface of an erosion and superficial telangiectatic patches indicate advisable fields for biopsy. It is far wiser to have a negative pathologic report than to have destroyed by cautery a region which may have been the site of an early malignant lesion without having taken a specimen for biopsy.

An erosion of the uterine cervix is an interesting and fairly common lesion. The usually accepted theory of the formation of erosions is that the squamous cell epithelium of the portio vaginalis becomes macerated by infectious debris and fluids and that cells of columnar type progress out from the endocervix and replace with a columnar celled covering the epithelium so macerated. Such an erosion is usually rather sharply limited on its outer border and its columnar celled surface is confluent with the covering layer of the endocervix. Yet the typical racemose glands of the endocervix are not always produced in the erosion and there is some question whether the nabothian cysts seen in the region of erosion may not be inclusion cysts produced by infolding of this abnormal tissue growth. Certainly many erosions are seen in which evidence of previous infection does not appear and the previously mentioned stage of maceration of the squamous layer is seldom encountered. Some erosions seem to grow by piling up of layers of cells, so that they may appear crowded into folds or tufts or into minute papillae so closely packed as to resemble the surface of clipped velvet. Various manifestations of infection and cyst formation do appear in association with some erosions but there are other erosions which seem to be an uncomplicated metaplasia, in which cells of columnar type have replaced squamous layers over a limited area. The basement cells, which formerly produced squamous cells for some reason produce columnar cells. Why should such metaplasia occur? Is the area of metaplasia an extension of columnar cells from the endocervix or are these columnar cells formed by the existing basement cells?

The hypothesis of cellular adaptation to an unfavorable environment<sup>7</sup> allows a speculative inference that a similar process may occur in the production of an erosion of the cervix.

The environment of the cervix is subjected to various influences, such as the hormonal variation of the host. The chemical reaction mentioned previously varies in its intensity with fluids discharged from the upper part of the genital tract and these fluids are derived from the endometrium. The stages of the menstrual cycle produce repeated rhythmical variations. Processes of metaplasia have been re-



ported<sup>2 3</sup> from such situations as the bronchus, gallbladder, stomach, pharynx, prostate and anus and over the exposed surface of a long-standing chronic inversion of the uterus

When the process of metaplasia occurs on the portio vaginalis of the cervix, the basal cells of the mucosa, which form the reproductive or functioning layer, seem to alter their product from the supposedly natural protective squamous type of epithelium to a more secretory glandular-like columnar epithelium and a so-called erosion is produced. The basal cells of both the columnar and the squamous types of tissues of the portio vaginalis are said to appear to be similar histologically

If such a process does occur and produce an erosion as a result of cellular adaptation to unfavorable environment, could not a hypothesis go further and assume that cellular adaptation to unfavorable environment of frequent recurrence might proceed to the production of the disorderly groups of cell arrangement found in "carcinoma in situ" or "noninvasive epithelioma"? If those tumors are truly malignant tissue, and evidence<sup>4, 8</sup> seems to be accumulating that they may develop into the more common examples of malignant process, they offer an earlier step in diagnosis than the commonly accepted stage 1 carcinomas of the cervix. Carcinoma in situ is not diagnosed except by the pathologist and no doubt many such carcinomas have been destroyed by cervical cautery when a specimen for biopsy was not obtained. Some reports indicate reduction in frequency of primary carcinoma of the cervix since cauterization has become more prevalent

Treatment of chronic cervicitis is aimed at eradication of the lesion. Actual destruction by some form of heat such as electric hot wire cautery is more commonly employed than surgical removal at the present time

*Cauterization by nasal tip cautery* is a convenient process and is performed under direct visualization. It may be an office procedure and the patient may remain ambulatory. Other processes of actual destruction of diseased tissue may be equally efficacious and may be preferred by some but actual cautery has the advantage of simplicity of equipment, of visual control of extent and of minimal complications. Burning should be done slowly with a dull red, rather than a bright yellow, wire loop and should extend to a depth just through the mucosa. The lines should be spaced closely enough together so that radiant heat coagulates the intervening tissue and turns it ash-white. Cysts are evacuated by cautery puncture and their lining membrane is coagulated. If severed small vessels tend to spurt or ooze, they are nearly always controlled with the cautery by holding the glowing tip against the bleeding point. Sometimes the bleeding is effectually stopped by cauterizing deeper in an adjacent line, thus reaching the vessel in deeper tissue. When the cervix is considerably thickened and the lips are everted and contain deeply buried cysts, the cautery incisions may

be deeper and extend farther into the substance peripherally, so that the shrinkage which results tends to restore the cervix to a more normal size.

Whether or not the endocervix should be cauterized depends on its involvement. In cases of simple superficial erosion there seems no good reason for destroying the endocervix and healing is completed in a shorter period if only a surface cautery is required. When the endocervix is involved and requires cauterization it should be quite thoroughly treated and the cautery lines from the endocervix should cut deeply at the os and extend to the periphery of the area to be cauterized on the portio vaginalis. The resulting fibrosis tends to result in an open os and is less likely to result in stenosis. The endocervix is not usually visualizable. When it is extensively involved, the procedure of conization may be preferable. However, this should be an operating room process and after conization there seems a greater incidence of subsequent hemorrhage and the need of frequent observation because of the tendency to stenosis.

After actual cauterization there occurs a heavy slough, which softens and produces a foul leukorrhea for four to six days but which has usually cleared off in about ten days. During the healing stage it is permissible to wipe the cervix with a mild antiseptic on a cotton applicator, a procedure which will help to prevent some of the bad odor and at the same time permit inspection of the cauterized area for small adherent clots of blood or bleeding points. These clots may be wiped away and an astringent solution applied. Healing and a new surface have organized in four to six weeks but subsequent involution may not be completed for perhaps six months. Examination by palpation and inspection seems worth while at a three months' and again at a six months' interval, particularly to ascertain whether all cysts have been destroyed and whether the lesion is completely healed and to determine the amount of involution ultimately obtained by the procedure. Complications are usually not severe. Postcautery bleeding during the sloughing off of the eschar may require attention for a few days and many minor processes are utilized to check bleeding of the areas. In some instances a packing of iodoform gauze may be required. When it is employed, it should be left in place for forty-eight hours, so that the removal of the gauze may not again open the bleeding vessel. Pelvic ache may be aggravated for a few days in some cases and occasionally an unsuspected subacute inflammation of the adjacent pelvic structures will flare up so as to produce febrile reaction. However, such reactions usually subside promptly. Urinary complications are at times temporarily aggravated. A tendency to cervical stenosis of the os occurs in some cases and may respond simply to dilatation. If it repeatedly recurs, an enlargement of the opening may be effected by a crossed incision through the os by means of the cautery wire.

## SUMMARY

A chronically diseased cervix may be the source of either local or more systemic symptoms. The causation of cervical erosions is an interesting field of speculation. The suggestion is offered that these erosions may perhaps be a manifestation of metaplasia resulting from cellular adaptation to unfavorable environment and that so-called carcinoma in situ may be a further step in such a metaplasia. The foregoing is only suggested as a speculation, for proof of such process seems lacking at the present time. However, erosions and other cervical lesions justify the taking of a specimen for pathologic analysis and the correction of lesions of chronic cervicitis seems to have assisted in a reduction of the occurrence of cervical malignant disease.

## REFERENCES

- 1 Benedict, W. L. Episcleritis and its relation to disease of the female pelvic organs. *Minnesota Med* 20:287-291 (May) 1937.
- 2 Broders, A. C. The grading of carcinoma. *Minnesota Med* 8:726-730 (Dec) 1925.
- 3 Broders, A. C. Personal communication to the author.
- 4 Macfarlane, Catharine, Sturgis, Margaret C. and Fetterman, Faith S. The value of periodic pelvic examination, in the control of cancer of the uterus. *J.A.M.A.* 126:877-879 (Dec 2) 1944.
- 5 Piper, M. C. Lesions of the uterine cervix. *M. CLIN. NORTH AMERICA* 19:347-357 (Sept.) 1935.
- 6 Piper, M. C. Four common conditions of the vagina and cervix. *Proc. Staff Meet., Mayo Clin* 11:689-691 (Oct. 28) 1936.
- 7 Spencer, R. R. Carcinogenesis and cellular adaptation, the George Chase Christian Lecture for 1944. *Bull. Minnesota M. Found* 5:1-7 (Nov) 1944.
- 8 TeLinde, R. W. and Galvin, Gerald. The minimal histological changes in biopsies to justify a diagnosis of cervical cancer. *Am. J. Obst. & Gynec.* 48:774-794 (Dec) 1944.

## CERTAIN CONDITIONS OF THE FEMALE URETHRA

EDWARD N. COOK AND JANE L. HODGSON

The purpose of this discussion is to review certain conditions of the female urethra from the standpoint of etiologic factors, symptoms, diagnosis and treatment. Such a discussion presupposes a thorough knowledge of the anatomy of this part of the body.

The female urethra is a short tubular structure, 3 to 5 cm. in length, extending from the bladder to the vestibule. In multiparas it is usually shorter than this. The external urethral meatus, which may be slitlike or may resemble an inverted Y, is usually the narrowest portion of the urethral canal. The urethral wall has a mucous, submucous and muscular coat. The epithelium lining the canal is of the stratified, squamous type except near the bladder where it becomes transitional in type, similar to that of the bladder. There are many small tubular glands in the proximal one third of the urethra and a few lesser ones in the outer third. On each side of the floor of the urethra just within the external meatus are the two openings of Skene's glands. In some instances the orifices of these glands may be in the vestibule adjacent to the external meatus. The submucosa is a layer of loose areolar tissue with some elastic fibers and a network of venous spaces. The muscular coat is composed of two layers, an inner longitudinal layer and an outer circular layer. The inner portion of the circular layer at the vesical outlet forms the involuntary sphincter of the bladder. The true voluntary sphincter is a layer of striated muscle fibers arising between the two layers of the triangular ligament, surrounding completely the urethra and extending proximally to the vesical outlet.

Since the urethral channel in the female passes directly from the bladder to the outside, it has a markedly inferior defense against ascending infection as compared with the urethral channel in the male. The external urethral meatus is in constant contact with vestibular and vaginal secretions and consequently there is the ever present possibility of organisms entering the urethra and setting up a distressing condition. The majority of infections of the urethra in the female are of this type.

Proper evaluation of the patient's complaint is of primary importance. At the Clinic patients are frequently encountered who have been taking a urinary antiseptic because of urinary symptoms and the finding of pus cells in a specimen of voided urine. No benefit has been derived from this treatment and further examination of a specimen of catheterized urine reveals no cellular elements. Such a situation should indicate the need for urethroscopic and cystoscopic investigation since proper evaluation of the patient's distress can be made only by this means.

## URETHRITIS

One of the most common maladies of the female is inflammation of the urethra. This lesion frequently is found in women more than forty years of age. The classic experiment of Winsbury White did much to explain the frequent association of urethritis and trigonitis with endocervicitis, and also the fact that urethritis frequently accompanies monilial, trichomonal, gonorrheal, puerperal and postabortive infections. White demonstrated the relation between the cervix of the uterus in guinea pigs and the trigone of the bladder. He injected India ink into the cervix uteri and later found the dye in the lymph spaces where the bladder and vagina are in intimate contact.

The most common symptoms of urethritis are frequency and burning on urination. Urgency and dysuria also may be present. In the more severe cases tenesmus is noted. These irritative phenomena usually are aggravated during micturition and many times reach their greatest severity immediately after the act is completed. Hematuria is not common but may be present. If symptoms of external irritation are present, they usually are caused by associated meatitis. Dyspareunia occasionally is encountered, particularly if there is an associated urethral diverticulum. Any or all of these symptoms may be present in the various types of urethral inflammation.

The remainder of the discussion of urethritis deals with two forms of this condition, namely, simple urethritis and senile urethritis.

**Simple Urethritis.**—This form of urethritis, which is by far the more common, can be divided into granular and cicatricial types with or without associated inflammatory tags. On urethroscopic examination of the granular type the mucosa is raised, reddened and has a granular appearance in scattered regions or throughout the whole urethra. Purulent secretion seldom is encountered. Frequently there is diffuse tightness of varying degree to the passage of the instrument along the canal. This may exist alone or in association with the granular change. At times a cicatricial process may have advanced to such a degree that there is a true stricture with symptoms of obstruction to the passage of urine as well as the objective findings of residual urine and trabeculation of the bladder.

In many cases of granular and cicatricial urethritis there are localized regions of mucosal proliferation, particularly at the vesical neck, which are referred to as inflammatory tags. These swollen reddened regions in themselves cause no particular difficulty and are only another manifestation of the granular change in the mucosa.

In the treatment of simple urethritis, the use of irritating medicines, frequent instrumentation and all forms of cauterization should be kept at a minimum. In the granular type, the use of a mild astringent such as argyrol, 5 per cent, or protargol, 1 per cent, applied once daily for a week on an applicator of cotton and left in place for five to ten minutes usually is of benefit. Warm sitz baths also should be taken daily.

If there is associated cicatricial change, the urethra should be dilated every two or three days until it readily admits a 30 F or 32 F sound. Fulguration of the urethra in the female is of little value and extensive treatment of this type often results in extreme inflammation and cicatrization.

At the Clinic this simple and mild type of treatment has proved most successful. It is important to emphasize to patients the benignity of the lesion and also the harm that can result from overtreatment. A proper understanding by the patient of her trouble will help her to tolerate the occasional mild recurrences.

**Senile Urethritis.**—Since senile urethritis is comparatively rare, it is frequently overlooked. The symptoms may be severe and yet the signs of urethritis may be mild. The urethral mucosa may present a thinned out and somewhat reddened appearance similar to that of the mucosa of the vagina when senile vaginitis is present. The onset of the urinary symptoms and the onset of the menopause usually are simultaneous. The administration of estrogens has been of great value.

#### PROLAPSE OF URETHRAL MUCOSA

In prolapse of the urethral mucosa there is eversion of the mucous membrane of the urethra through the meatus, resulting in a red, congested tumor-like mass at the external meatus. The condition is important because it is frequently confused with caruncle of the urethra, which will be discussed in the next paragraph. Prolapse of the urethral mucosa probably is due to certain cicatricial changes which result from long-standing chronic inflammation of the urethra and meatus. The prolapsed region may bleed easily and is frequently the site of associated meatitis. Local tenderness and burning on urination often are noted. Treatment is essentially the same as for granular urethritis, with dilatation of the urethra if indicated and the use of mild astringent ointments locally if the meatus is inflamed.

#### CARUNCLE

Caruncle, which is a mucous polyp usually arising from the posterior aspect of the urethral meatus, frequently is confused with prolapse of the urethral mucosa, as previously mentioned. It is usually single but may be multiple. As a rule, a caruncle is exquisitely tender, fragile and bleeds easily, and at times the lesion is incapacitating. It may be papillomatous or angiomatous depending on its histologic structure. Treatment is best carried out by excision either by clamp or by scissors and cauterization of the base by scarring with mercuric nitrate, according to the method of Crenshaw. O'Connor advised electric desiccation with a needle electrode, care being taken to coagulate the entire base of the caruncle without destroying the surrounding tissue.

## URETHRAL DIVERTICULUM

Many causes have been recorded as being responsible for urethral diverticulum. This condition probably is acquired and may arise from infected periurethral glands. The symptoms are much the same as those encountered in cases of simple urethritis but frequently are more severe. Occasionally, swelling may be palpated in the anterior vaginal wall which on pressure produces a discharge from the urethral orifice. Pain on walking and dyspareunia occasionally are noted.

The diagnosis is made by demonstration of the pocket with an opaque medium. On cystoscopic examination one or more minute scarred openings may be seen in the floor of the urethra. If possible, a soft 4 F ureteral catheter is passed into the opening and coiled in the pocket. Opaque medium then is injected and a roentgenogram made. At times a mass in the anterior vaginal wall may be palpated. The urethral diverticulum occasionally may contain calcareous material.

The treatment is surgical. Local therapy in the form of strong astringent solutions or fulguration are only rarely of value. Surgical excision of the pocket through a vaginal approach, with careful closure of the urethral opening and repair of the urethral floor usually are necessary to relieve this distressing complaint.

# REAL VERSUS SUPPOSED DISTURBANCES OF THE ENDOCRINE GLANDS

EDWARD H RYNEARSON

MANY physicians have had the opportunity to observe "endocrinology" almost from its beginning to its present state. The term "endocrinology" was applied to the study of the endocrine glands at a time when not all of the glands were recognized and when few of their functions were known. These physicians can remember when tablets of whole pancreas were prescribed for diabetes, when epinephrine was the treatment for Addison's disease and when ovarian residue was prescribed for the menopause. They have lived to see the recognition of more of these glands and the delineation of many of their functions. Yet endocrinology still is not a science and still is but a part, though a most intriguing part, of internal medicine.

As knowledge has increased, better definitions of certain disturbances of the endocrine glands have been possible. What are some of these?

## THE POSTERIOR LOBE OF THE PITUITARY

This small amount of tissue produces two hormones. One is pitocin which stimulates the contraction of the uterus and is useful for certain obstetric conditions. The other is pitressin which induces peripheral vasoconstriction and stimulates smooth muscle. It has an important antidiuretic effect. No known syndrome has been established that is due to the overproduction of the hormones of the posterior pituitary.

*Diabetes insipidus* is caused by the underproduction of the posterior pituitary and the consequent absence or decrease of its antidiuretic effect on body tissues. The many possible etiologic factors are described in the excellent observations of Ranson and his associates.<sup>6</sup> The symptoms of diabetes insipidus need no review. The treatment consists in the replacement of pitressin by one of three methods. The first is the use of pitressin in aqueous solution, the disadvantages of which are the expense, the annoyance of multiple hypodermic injections and the sometimes unpleasant side effects due to stimulation of smooth muscle. The second method, the use of pitressin tannate in oil, has the advantage over the first method of delayed absorption which necessitates fewer injections. The third, and method of choice, is the nasal insufflation of powdered whole posterior lobe. Almost never does a patient find this method irritating to the nasal membranes and the patient prefers it to the other two methods because of its ease of administration, its relative inexpensiveness and the absence of unpleasant side effects. Few patients need more than an application of powder in the morning and evening and they learn to measure on the end of a



small blade or nail file the amount which is to be snuffed or blown into the nares

Some patients who are "supposed" to have diabetes insipidus, in reality, are only nervous water drinkers. For one reason or another their habit of drinking large quantities of water or other fluids has developed. Only occasionally do they drink as much as the patient who has diabetes insipidus and practically never do they drink as much during the night. A patient who has diabetes insipidus may drink as much or more during the night as during the day. Such a patient may arise eight or ten times during the night to urinate and drink, the nervous water drinker rarely presents this history. The concentration test,<sup>4</sup> easily performed, determines the diagnosis since the nervous patient concentrates urine normally, but the patient who has untreated diabetes insipidus cannot concentrate urine to above a specific gravity of more than 1.010.

#### THE ANTERIOR LOBE OF THE PITUITARY

This small gland has only two types of secreting cells, the acidophil cells and the basophil cells. There is no known secretion from the chromophobe cells. Physicians are asked to believe that these two types of cells are capable of secreting a large number of distinct hormones, such as one or more gonadotropic hormones and hormones essential for growth, the function of all the other endocrine glands and the utilization of food and water. There is no question about the importance of this gland in the growth, maturation and function of the body, there is serious doubt as to whether this is accomplished through the production of so many distinct hormones. These matters have been summarized completely in another publication.<sup>2</sup>

Clinically, there are not many recognized disturbances of this gland. Underfunction, underdevelopment or removal prior to puberty produces the clinical picture of *dwarfism* or *infantilism*, underfunction or removal after puberty results in the syndrome of *hypopituitarism*. There are, of course, many variations but the condition which follows the surgical removal of the gland is well known to all physicians. Some have seen one of the rare cases of *Simmonds'* or *Sheehan's syndrome* which follows the destruction of the anterior pituitary gland. These occur most often in women who have had a severe hemorrhage or shock after childbirth. All have seen the clinical picture which follows the destruction of the pituitary due to adenoma of the chromophobe cells. These typical examples are mentioned because often the diagnosis of pituitary insufficiency is made on insufficient data. Many fat boys have the clinical picture known as *Frohlich's syndrome* but few have any organic disease of the pituitary, most patients whose condition is diagnosed as *Simmonds'* disease are really suffering from *anorexia nervosa* and certainly few undersized individuals are suffering from pituitary insufficiency.

Unfortunately, the treatment of pituitary insufficiency is unsatisfactory. A recent review of the literature<sup>11</sup> revealed that the clinical use of the anterior pituitary hormones has been disappointing. Since commercial growth hormones have not helped in the treatment of true pituitary dwarfism why should anyone expect them to prove of value in the treatment of the undersized individual who is usually the child of small parents. There are two main objections to the use of anterior pituitary extracts (1) They are rarely and only temporarily effective and (2) there is good evidence that administration of these hormones results in the production of antihormones which render the treatment ineffective. This does not mean that the careful, critical use of such hormones should be stopped entirely but their widespread use does not seem justified by evidence. Some patients have been helped by the use of the extracts of those glands which are nonfunctioning as a secondary result of pituitary failure. Thyroid, adrenal and male or female sex hormones are sometimes helpful but often results of their use are disappointing. Gonadotropic hormones obtained from the urine of pregnant women (chorionic gonadotropins) or from the serum of pregnant mares (equine gonadotropins) are pituitary-like in character and have had more extensive clinical use than anterior pituitary hormones. Their use for males, particularly in the treatment of undescended testes, has been reported by many observers. The administration of either or both in the treatment of women likewise has been reported frequently.

Overfunction of the anterior pituitary gland produces a syndrome which depends on the age of the individual and the type of hormone being produced in excess. Thus an excess of growth hormone, supplied before ossification is complete produces *gigantism*, after this, it produces *acromegaly*. Many patients who have an excess of the growth hormone can be treated successfully by roentgen rays to the pituitary. If changes in the visual fields are present and progressive, the surgical removal of the gland is advisable.

But again, a true glandular disturbance is not present in every "supposed" case. The sixteen year old girl who is 5 feet 10 inches (177.8 cm.) tall and well proportioned is probably entirely normal and certainly needs help only in making a philosophical adjustment to her height. Many women are supposed to have a basophilic adenoma simply because of obesity and hirsutism. There are thousands of fat, hairy women with irregularity or absence of menses but not one in a thousand has true Cushing's syndrome. In the light of our present knowledge the other 999 need a frank discussion, instruction concerning a regimen for reduction of weight and advice concerning the cosmetic treatment for the excess hair. Many women who have had help in losing excess weight and disfiguring hair are again happy members of society.

*Pituitary basophilism*<sup>8</sup> (Cushing's syndrome) is rare and serious. If

it occurs in a girl prior to puberty, she will undergo premature maturity, may menstruate, develop large breasts, and so forth, if it affects a woman, amenorrhea and masculinizing changes follow. In both a peculiar obesity will involve the trunk with the Buffalo hump across the shoulders and the arms and legs are relatively thin. The skin is often plethoric and covered with acne and hair. Wide purplish striae are present. Examination shows variations of hypertension, osteoporosis, polycythemia, glycosuria, hyperglycemia and elevation of the basal metabolic rate. The picture is comparable in many respects to that produced by a tumor of the adrenal cortex or an arrhenoblastoma of the ovary. Once these conditions have been excluded, the only treatment is roentgen therapy to the pituitary.

After such treatment, many months pass before any improvement may result and only too often the whole sad picture may recur after it has seemed to disappear completely. The seriousness of this condition is an important reason for careful application of the term, records are available of patients who have committed suicide after receiving this diagnosis.

#### THE THYROID

Only a small fraction of the thyroid extract which is manufactured commercially is used for the treatment of *myxedema*, most of it is used for conditions which are "supposed" to be associated with a lack of this hormone. Myxedema responds excellently to administration of thyroid extracts. Because myxedema is a clear-cut entity caused by the lack of a single hormone, the administration of a small amount of thyroid extract completely controls the condition. I have not seen any patient with myxedema who required more than 2 grains (0.13 gm) of desiccated thyroid extract per day and the addition or subtraction of even  $\frac{1}{4}$  grain (0.016 gm) is reflected in the patient's condition and basal metabolic rate. I have never seen a patient with uncomplicated myxedema who could not tolerate the use of thyroid extract, although many of these patients have unpleasant symptoms, such as generalized aches and pains, for the first few weeks of treatment. Very rarely thyroid extract cannot be administered because of the coexistence of a serious condition, such as severe angina pectoris.

Contrast this with all the patients with "supposed" thyroid deficiency. One such patient has a low basal metabolic rate ( $-16$  per cent) and she complains of being chronically tired. "I feel low all the time," she states. Her basal metabolic rate is not all that is low, so may be her hemoglobin, blood count, blood pressure and gastric acids. Many organs may be low including a "dropped stomach," "dropped colon," "dropped kidneys" and a retroverted uterus. Yet the treatment that is most likely to be tried first is administration of thyroid extract. After she has taken 5 grains (0.3 gm) daily for five weeks her basal metabolic rate is found to have risen only to  $-14$  per cent.

This exaggerated hypothetical case can be reproduced, with variations, in the experience of all physicians. Nothing that can be said or done will affect this abuse. Use of thyroid extract should not be limited to the treatment of myxedema for often it helps other conditions and it is often only by trial that this can be determined. Often it helps in the management of obstetric and gynecologic cases in which the indications for its use are not too well defined. However, if its use is ineffective, it should be stopped. The abuse of thyroid extract in the treatment of obesity is well recognized. To date, 48 grains (3.2 gm.) of desiccated thyroid extract daily is the largest dose that I have found any patient taking.

The syndromes of overfunction of the thyroid are also easily recognized. All physicians can make a mistake in diagnosis but there is little general abuse of the diagnosis of *hyperthyroidism*. The use of strong solution of iodine followed by thyroidectomy constitutes most satisfactory treatment. The occasional recurrence and the still more infrequent development of severe postoperative complications of the eyes remain the chief discouragements. Much interest has followed the publication by Astwood<sup>2</sup> of treatment with chemotherapeutic agents. Some observers are of the opinion that thiouracil or an allied substance eventually may replace the use of surgical procedures and they may. At present most observers are finding their use an excellent method for the preoperative care of certain patients and for the sole treatment of a few patients for whom operation cannot be advised.

#### THE PARATHYROID GLANDS

A separate article in this number deals with hyperparathyroidism and this condition will not be discussed here.

*Parathyroid insufficiency* occasionally occurs spontaneously, but far more frequently follows the injury to, or removal of, the parathyroid glands at the time of thyroidectomy. After this accident or spontaneously the level of calcium in the blood decreases and that of phosphorus increases. The symptoms which are well known consist of nervous excitability with positive Chvostek's and Trousseau's signs, muscular spasms, particularly of the extremities, and numbness and tingling, particularly about the lips. Usually the condition is easily recognized, readily confirmed and rapidly responds to treatment. The treatment consists in increasing the concentration of calcium in the blood. Parathyroid hormone is rarely used because it is expensive and may be dangerous if its uncontrolled use is prolonged. Calcium chloride or calcium gluconate can be given *extensively* if the need is urgent. In most cases the condition can be controlled by the steady and inexpensive use of calcium by mouth with vitamin D to aid in its absorption in the intestine. A teaspoonful of calcium lactate or calcium gluconate (4 gm.) administered *every 4 or 6 hours* for more frequently (if necessary) will control parathyroid insufficiency in almost every case.

If calcium lactate is used, it should be stirred in boiling water until a clear solution results, since it is poorly absorbed if it is not in solution. Calcium tablets are much less effective. Vitamin D can be given by mouth twice daily.

Two other substances which should be mentioned are calciferol (vitamin D<sub>2</sub>) and dihydrotachysterol (A T 10). These are crystalline products obtained by the irradiation of ergosterol. They are effective when given by mouth and are extremely potent. As in the use of the parathyroid hormone, care should be exercised to avoid overdosage.

### THE PANCREAS

The chief endocrine function of the pancreas is, of course, the production of insulin. The role of its other endocrine and excretory products will not be discussed in this paper. *Diabetes mellitus* usually is recognized easily and the treatment with diet and some type of insulin is well understood. The only condition which may be confused with diabetes mellitus which I will mention is that of the patient whose urine shows some reducing substance and whose blood sugar is normal. If a sugar tolerance test is performed and the result indicates decreased tolerance for sugar, then the diagnosis of diabetes mellitus appears on the patient's record. From that moment on it will be difficult, and sometimes impossible, for the patient to obtain life insurance, if insurance is issued, it is with increased premiums. One such patient returned to the Clinic and the results of repeated sugar tolerance tests were normal. Life insurance finally was granted. The sugar tolerance test is not a specific test for the presence or absence of diabetes. It is affected by absorption, by obesity, by the patient's diet, by many disturbances of the liver and muscles and by the various endocrine glands. Even when the test on a thin person who has been on a high carbohydrate regimen is positive the interpretation may be questioned. In cases of the type under consideration in which the level of the blood sugar is normal, the patient can be as well protected by discussing the need for further observation as by doing a sugar tolerance test. This test is of much more importance when it gives a negative result than when the result is positive. When the result is questionably positive the diagnosis should be deferred.

In contrast to definite diabetes mellitus is *hyperinsulinism*. The first proved instance of this disease was reported in 1927<sup>1</sup> and the total number of proved cases is probably less than 200, yet the literature contains reference to thousands of supposed cases. A patient who has proved hyperinsulinism usually has clear-cut symptoms of a severe insulin reaction occurring only when he is fasting or has been exercising. His blood sugar readings at such times are very low. He obtains prompt relief from the administration of carbohydrate and all symptoms disappear completely after the successful removal of an insulin producing adenoma of the pancreas. Unfortunately, the term "hyper-

insulinism" is applied to the condition of many patients whose symptoms are bizarre, who do not have low values for fasting blood sugar, who obtain questionable relief from the administration of carbohydrate, whose sugar tolerance curves may be flat and who usually can better be described as suffering from neurocirculatory asthenia or chronic nervous exhaustion. If the criteria as defined by Whipple<sup>13</sup> are followed in making the diagnosis, confusion in the use of the term will be less severe.

### THE SEX GLANDS

There is little difficulty in the diagnosis of conditions arising from overfunction of the sex glands. These conditions are the result of tumors or hyperplasia of the ovaries or testes. The most common one is an *arrhenoblastoma of the ovary* which produces the clinical picture comparable to a tumor or hyperplasia of the basophilic cells of the pituitary (Cushing's syndrome) or a tumor of the adrenal cortex.

There is much more difficulty in making the diagnosis of underfunction. From the earliest days of medical history there are references to the *female menopause* and it is only within recent years that successful treatment of the accompanying symptoms has been possible. New diagnostic aids are available such as assays of the hormones in the urine (and blood) and study of the vaginal and endometrial cells. Physicians are no longer entirely reliant on the patient's story for diagnosis. It will be years, if ever, before treatment is standardized and each physician is partial to his own plan for the use of natural or synthetic estrogens in the treatment of the menopause. Other endocrine products, including testosterone propionate, thyroid, pituitary and pituitary-like hormones, are being used.

The references in medical literature to the *male menopause* have increased tremendously since testosterone propionate was made available. If the male menopause is really so common, why was it not more discussed in the past? If, as is sometimes stated, it is as common as the female menopause, why has it been mentioned so rarely? No one questions its identity, many question its incidence. When male hormone is administered in questionable cases and good results follow, the conclusion is that the treatment confirms the suspicion. Yet critical studies indicate that many such patients receive as much improvement from placebos. Sexual impotence is more often than not psychogenic and relief from any treatment may be the result of psychotherapy. The exhaustion and fatigue of the tired business man is more likely related to a lack of competent assistance in his business than to a lack of hormone. When the number of "forms to fill out" decreases there will be a decrease in the incidence of the "male menopause." A patient with genuine male menopause or a eunuch will be greatly benefited by the administration of the male hormone. Not only will he feel better, but there will be an increase in musculature, deposition of bone

and other objective findings, both laboratory and clinical, such as more normal sex response, lowering of the voice, improvement in genital development, condition of the skin, hair and so forth. To repeat, I question only the incidence of the male menopause.

#### THE ADRENAL MEDULLA

There is no known syndrome associated with the underfunction of the adrenal medulla.

Paroxysmal hypertension is usually due to an adrenal medullary tumor, a *pheochromocytoma*. This is the rarest of all tumors of the endocrine glands. The usual history is one of sudden, marked rises of the blood pressure with severe vasomotor symptoms due to the paroxysmal outpouring of large amounts of adrenin from the tumor. Roth and Kvale<sup>10</sup> have described the use of histamine to establish the diagnosis. A single injection of a small amount of histamine produces a typical attack. The treatment is, of course, the surgical removal of the tumor, during the operation care must be exercised not to produce another attack. To do this manipulation of the tumor must be avoided until the vessels are clamped.

#### THE ADRENAL CORTEX

*Addison's disease* is, of course, the result of destruction of the adrenal cortex from tuberculosis or of simple atrophy. All physicians have seen cases of Addison's disease and recognize the pigmentary changes (not always present), the loss of weight and strength, the lowering of the level of sodium, chlorides and sugar and the elevation of potassium and urea in the blood, and the signs and symptoms of acute adrenal failure. Treatment consists in substitutional therapy, replacing the necessary electrolyte constituents and administering available hormones. Theoretically, the ideal treatment should be the administration of a whole adrenal cortical extract. The chief obstacles in this treatment are, first, the expense and, second, the fact that the extracts are not as potent as seem desirable. The time may come when a more potent, less expensive extract will be available. The extract from the adrenal glands of hogs may prove more active since this extract contains more of the "blood sugar raising" principle than do present commercial products. The only synthetic hormone of the adrenal cortex which has had extensive clinical use is desoxycorticosterone acetate<sup>12</sup> which can be administered hypodermically, by subcutaneous implantation of pellets, by the usual oral method or sublingually. This hormone is the most potent "salt and water retaining" hormone of the cortex but has no "blood sugar raising" effect. It has two disadvantages, first, the expense and, second, its incompleteness. If synthetic hormones are to be used, a mixture of desoxycorticosterone acetate with other fractions which will aid in other functions

(carbohydrate metabolism, for example) is needed. To date corticosterone and Kendall's fraction E are not available for clinical trial.

Certainly too much valuable hormone is being wasted in the treatment of patients whose condition cannot be diagnosed as adrenal cortical failure. I confess to being "allergic" to the term "subclinical" which is used frequently when adrenal cortical failure cannot be diagnosed definitely. There is no doubt but that there are different grades of severity of any disease but it is doubtful whether the use of adrenal

TABLE 1—SYNDROMES ASSOCIATED WITH DISTURBANCES OF ENDOCRINE GLANDS

Gland	Overproduction	Underproduction
Posterior pituitary	None known	Diabetes insipidus
Anterior pituitary	Gigantism, acromegaly, Cushing's syndrome	Dwarfism, Infantilism, Fröhlich's syndrome (?), Simmonds' disease (cachexia), Sheehan's syndrome
Thyroid	Adenomatous goiter with hyperthyroidism and exophthalmic goiter	Myxedema, cretinism
Parathyroid	Hyperparathyroidism	Parathyroid insufficiency
Pancreas	Hyperinsulinism	Diabetes mellitus
Adrenal medulla	Paroxysmal hypertension	None known
Adrenal cortex	Hyperadrenal cortical state	Addison's disease
Sex glands	Teratoma and Leydig's cell tumor (male) arrhenoblastoma, granulosa and theca cell tumors (female)	Menopause and other clinical pictures resulting from deficient function of the sex glands eunuchoidism

cortical hormone in any form is advisable unless there is evidence of failure of this gland. Tests are available for use in doubtful cases<sup>5, 6</sup>

#### COMMENT

In this brief article attention has been given to some of the real and some of the "supposed" disturbances. An excellent summary of other supposed disturbances is given by Relfenstein as follows:

"1 Fat boys with genitalia 'lost' in fat usually do not have Fröhlich's syndrome.

"2 Mental defectives have normal endocrine glands

"3 Congenital disorders (Mongolian idiots, Laurence-Moon syndrome, etc.) are congenital but not endocrine disorders

"4 'Spotty' syndromes (alopecia areata, Paget's



fibrosa disseminata, etc ) are 'spotty', but hormones do not affect one arm and not the other!

"5 End-organ unresponsiveness does not mean abnormal glands (American Indians do not raise beards)

"6 Obesity is not 'typed' according to glands, it usually results from polyphagia and abulia and not endocrine dysfunction

"7 Normal endocrine glands characterize most psychopathic (homosexual, etc ), psychoneurotic or psychotic persons

"8 Obscure diseases usually are not made lucid by incriminating the endocrines"

#### SUMMARY

The real disturbances are summarized in table 1

#### REFERENCES

- 1 Allan, F N Carcinoma of the islands of the pancreas with hyperinsulinism, report of a case Proc Staff Meet., Mayo Clin 2 88 (Apr 27) 1927
- 2 American Medical Association Council on Pharmacy and Chemistry Glandular physiology and therapy, a symposium prepared under the auspices of the Council on Pharmacy and Chemistry of the American Medical Association, Chicago, American Medical Association, 1942, 571 pp
- 3 Astwood, E B Treatment of hyperthyroidism with thiourea and thiouracil J.A.M.A. 122 78-81 (May 8) 1943
- 4 Brown, W E., Jr and Ryneerson, E H Procedure for diagnosis of diabetes insipidus Proc Staff Meet., Mayo Clin. 19 67-78 (Feb 9) 1944
- 5 Cutler, H H., Power, M H and Wilder, R. M Concentrations of chloride, sodium and potassium in urine and blood, their diagnostic significance in adrenal insufficiency J.A.M.A. 111.117-122 (July 9) 1938
- 6 Fisher, Charles, Ingram, W R. and Ranson, S W Diabetes insipidus and the neuro-hormonal control of water balance a contribution to the structure and function of the hypothalamico-hypophyseal system Ann Arbor, Michigan, Edwards Brothers, Inc., 1938, 212 pp
- 7 Gorsuch, M T and Ryneerson, E H Hyperinsulinism the use and misuse of the term. M CLIN NORTH AMERICA (July) 1944, pp 985-990
- 8 Kepler, E. J, Dockerty, M B and Priestley, J T Adrenal-like ovarian tumor associated with Cushing's syndrome (so-called masculinovoblastoma, luteoma, hypernephroma, adrenal cortical carcinoma of the ovary) Am J Obst & Gynec 47 43-62 (Jan) 1944
- 9 Robinson, F J, Power, M H and Kepler, E J Two new procedures to assist in recognition and exclusion of Addison's disease a preliminary report. Proc. Staff Meet., Mayo Clin 16 577-583 (Sept. 10) 1941
- 10 Roth, Grace M and Kvale, W F Unpublished data
- 11 Ryneerson, E. H Hormones of the anterior lobe of the pituitary body, a clinical review J.A.M.A. 125 5-9 (May 6) 1944
- 12 Thorn, G W, Dorrance, S S and Day, E Addison's disease, evaluation of synthetic desoxycorticosterone acetate therapy in 158 patients Ann Int. Med 16 1053-1096 (June) 1942
- 13 Whipple, Allan Quoted by Wilder, R M Clinical diabetes mellitus and hyper-insulinism Philadelphia, W B Saunders Company, 1940, pp 358-362

# THE DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM

F RAYMOND KEATING, JR.

THE emergence of hyperparathyroidism as a clinical entity is a comparatively recent event. It was unfortunate, but inevitable, that hyperparathyroidism should first be identified in cases of a disorder of bone known as osteitis fibrosa cystica. This circumstance has given rise to two erroneous concepts regarding this disease: first, that it is a great rarity, and second, that it inevitably occurs in association with osteitis fibrosa cystica. The first misconception springs from the second, and the second is a natural consequence of the history of the disease.

Von Recklinghausen<sup>10</sup> described osteitis fibrosa cystica in 1891. Askanazy<sup>12</sup> and later Erdheim<sup>9</sup> noted the association of this disease as well as other malacic diseases of bone with enlargement of the parathyroid glands. That adenoma of the parathyroid glands could be the cause of osteitis fibrosa cystica was not proved until 1925, when Mandl<sup>18, 27</sup> successfully treated this condition by excising a parathyroid adenoma. DuBois and his associates,<sup>21</sup> a year later, showed that the chemical and clinical abnormalities observed in a case of von Recklinghausen's disease were identical with those which followed the administration of an excess of parathyroid hormone to experimental animals. Barr and his colleagues,<sup>16</sup> in 1929, was the first in this country to report the successful removal of a parathyroid adenoma from a patient with osteitis fibrosa cystica. Similar reports appeared thereafter with increasing frequency.

In 1930, Bauer, Albright and Aub<sup>15</sup> reported the first of a series of important observations on the clinical and physiologic aspects of hyperparathyroidism. To a remarkable and unparalleled degree, these investigators have pioneered the subsequent studies of this condition. In 1934, Albright, Aub and Bauer<sup>5</sup> called attention to the frequency with which renal calculi occurred in cases of hyperparathyroidism and osteitis fibrosa cystica, and they demonstrated that hyperparathyroidism could occur and be recognized in cases in which there was no evident disease of bone. By 1937, Albright, Sulkowitch and Bloomberg<sup>6</sup> could report thirty-five cases of proved hyperparathyroidism, in twelve of which there was no evidence whatever of skeletal involvement.

Albright and Bloomberg<sup>2</sup> in 1934 were the first to show that renal disease was a more common manifestation of hyperparathyroidism than was disease of bone. The surgical management of parathyroid disease was thoroughly developed by Churchill<sup>21</sup> and Cope.<sup>23</sup> The pathologic changes of the parathyroid glands in cases of hyperparathyroidism were studied by Castleman and Mallory,<sup>19</sup> of Boston, who with Albright, Sulkowitch and Bloomberg<sup>7</sup> have reported a total of seven cases of primary hypertrophy of the parathyroid glands an-

entity not thus far encountered elsewhere. As judged by published case reports, hyperparathyroidism has remained a rare disease and generally is recognized only in the presence of extensive disease of bone.<sup>32</sup> By contrast, by 1942, Cope<sup>24</sup> and Albright were able to report a total of sixty-seven cases in which the presence of hyperparathyroidism was proved at operation, a series far larger than that observed by any other group of investigators. I am happy to acknowledge, therefore, that I have drawn freely from the observations and experience of Albright and his associates.

The first case of hyperparathyroidism observed at the Clinic was reported by Wilder<sup>40</sup> in 1929. For many years, the diagnosis was made very infrequently. Alexander, Kepler, Pemberton and Broders<sup>10</sup> in 1944 were able to collect only fourteen cases of proved hyperparathyroidism that had been observed at the Clinic in a period of fourteen years, namely, from January, 1929 to September, 1942. Considering the much greater incidence of the disease encountered by Albright and his associates at Boston, it appeared reasonable to assume that, at the Clinic as well as elsewhere, the presence of the disease was being overlooked. It seemed possible that the criteria which we had established for the diagnosis of this disease were unduly rigid. Early in 1943, a definite attempt was made to improve diagnostic accuracy by soliciting the co-operation of internists, urologists and surgeons.

In a period of approximately two and a half years, that is, from September, 1942 to January 31, 1945, inclusive, the presence of hyperparathyroidism was proved by operation in twenty-four cases. This is in marked contrast with the fourteen cases in which the presence of the disease was proved in the previous fourteen years. Our findings in the twenty-four cases fully confirm the observations of Albright and his associates. In seven, or 29 per cent, of the twenty-four cases, there was a clinical picture of classic osteitis fibrosa cystica. Minimal lesions of the skeleton were present in nine, or 38 per cent, of the cases but in eight, or 33 per cent, of the cases there was no evidence whatever of osseous lesions.

#### PRIMARY HYPERPARATHYROIDISM

Hyperparathyroidism is classified as secondary when it results from compensatory hyperplasia of the parathyroid glands due to some other disease such as nephritis or rickets. It is classified as primary when no such etiologic factor is present.

Primary hyperparathyroidism is nearly always caused by one or, occasionally, two adenomas of the parathyroid glands. The tumors which produce hyperparathyroidism are small and more often than not are impalpable. They may occur retrosternally and may be overlooked even when the neck is explored surgically. There are a number of instances in which two or even three operations have been necessary before the tumor could be located.

Hyperfunctioning parathyroid tumors which show unequivocal clinical evidences of malignancy are exceedingly rare.<sup>20 30</sup> Alexander and his associates<sup>10</sup> described cytologic changes, which in their opinion warranted a diagnosis of adenocarcinoma in twelve of the fourteen parathyroid tumors in their series. Castleman and Mallory,<sup>10 20</sup> on the other hand, have regarded all of the parathyroid tumors which they have observed as benign adenomas. Irrespective of the pros and cons of the pathologic interpretation of these tumors, it is generally agreed by all investigators that the great majority of such tumors lack the biologic characteristics of malignant lesions. These tumors rarely recur, invade or metastasize, but there have been a very few isolated instances to the contrary.

Cope<sup>25</sup> and Albright have observed seven cases in which primary hyperparathyroidism was associated with a curious enlargement of all four parathyroid glands. Histologically, the glands were composed of giant water clear cells. Secondary hyperparathyroidism, on the other hand, is accompanied by hyperplasia of the chief cells.<sup>20 43</sup>

**Symptoms**—Primary hyperparathyroidism is protean and most variable in its clinical manifestations. Albright<sup>1</sup> divided the symptoms which may be encountered into three groups: (1) symptoms produced by the chemical changes in the blood, (2) symptoms produced by involvement of the urinary tract and (3) symptoms produced by involvement of the skeleton.

*Symptoms Resulting from the Chemical Alterations in the Blood*—Hyperparathyroidism is characterized by hypercalcemia and hypophosphatemia. These findings are the reverse of those encountered in parathyroid tetany. One would expect, therefore, to encounter symptoms which represent the converse of tetany and this is, indeed, the case. Pronounced muscular atony occurs and, with it, weakness, fatigue, constipation, anorexia, loss of weight, nausea and vomiting are sometimes encountered. Excepting in instances of severe hypercalcemia, these symptoms may be vague and in cases in which there is minimal alteration of the chemistry of the blood they often are absent. Changes in the electrocardiogram and in the electric excitability of skeletal muscle have been described by DuBois and his associates.<sup>31</sup>

*Symptoms Resulting from Involvement of the Urinary Tract*—Such symptoms may be due to (1) chemical changes in the urine per se, (2) the formation of renal calculi and (3) the production of parenchymatous renal disease.

Uncomplicated hyperparathyroidism always produces hypercalcemia and hyperphosphaturia. This excessive loss of minerals is accompanied in some instances by conspicuous polyuria and polydipsia. At times these are so severe as to lead to a mistaken diagnosis of diabetes insipidus. Polyuria is not universally present, however, and its presence or absence cannot be correlated with the degree of calcinuria which is present. Even when a significant degree of polyuria is absent,

in our experience the urine usually is found to have a low specific gravity

Excessive excretion of calcium and phosphorus leads to the formation of renal stones in a high proportion of cases. In twenty, or 80 per cent, of twenty-four cases observed in the past two years, renal calculi were present. As one would expect, some of the stones were composed of calcium phosphate but, for reasons not understood, most of the stones contained calcium oxalate. The stones which occur in hyperparathyroidism may produce all the symptoms and complications common to renal calculi from any source.

In some cases, calcium is deposited in the renal substance, probably in the renal tubules. This results in nephrocalcinosis, a diffuse calcification of the renal parenchyma associated with sclerosis and destruction of renal substance which may progress to a stage where serious renal insufficiency occurs. The condition is generally regarded as irreversible even though the hyperparathyroidism is eliminated. Baker and Howard<sup>14</sup> have reported a case of hyperparathyroidism, nephrocalcinosis and renal insufficiency in which, after excision of a parathyroid tumor, a remarkable degree of recovery at first took place. Severe hypertension developed later and the patient died of a dissecting aneurysm.<sup>88</sup>

A serious degree of renal insufficiency can, of course, result from pyelonephritis or hydronephrosis caused by renal calculi. Pyelonephritis and nephrocalcinosis make damage to the kidney by far the most important consequence of hyperparathyroidism and are ample justification (if such be needed) for seeking means of improving diagnostic methods.<sup>8</sup>

*Symptoms Resulting from Involvement of the Skeleton*—In many cases in which the absorption of calcium from the diet is approximately equal to that lost through the urine, no evident change occurs in the skeleton. In other cases, there may be any degree of skeletal involvement from minimal demineralization to the most profound depletion and disarrangement of the entire skeleton which are characteristic of advanced osteitis fibrosa cystica. Patients with minimal skeletal changes may have no symptoms whatever or, at the most, may have vague aching and pain.

In cases in which the disease is advanced, various tumors, cysts, pathologic fractures and deformities may occur and be accompanied by intense pain and discomfort. Favorite sites for such lesions are the long bones, ribs, pelvis, and the metacarpal and metatarsal bones. Brown tumors of the jaw, so-called epulis, are often but not invariably indicative of this disease. Loss of height, kyphosis and other deformities of the skeleton may be observed.

Pathologically, the osseous lesions show extensive resorption and decalcification of bone with much fibrous proliferation, but the most conspicuous feature is the intense cellular activity resulting from in-

crease in the numbers of both osteoblasts and osteoclasts. Tumors, when encountered, are generally composed of osteoblasts or osteoclasts and usually are described as giant cell tumors. Cysts filled with clear fluid are common, but many of the cystic lesions observed on roentgenographic examination are actually cellular masses.

*Signs and Symptoms Encountered in Cases of Mild Hyperparathyroidism.*—A perusal of the foregoing account may prove of little value in making the diagnosis of hyperparathyroidism in the majority of cases. Most of the symptoms which have been noted are often absent. The full range of symptoms is to be encountered only in a case of severe "classic" osteitis fibrosa cystica. Even in such a case there is infinite variation as to the occurrence and severity of symptoms. Our recent experience at the Clinic substantiates Albright's observations that cases of "classic" hyperparathyroidism with osteitis fibrosa cystica are a distant minority compared with the large group of cases in which evidence of involvement of bone is minimal or lacking. In the latter cases, not only are all symptoms referable to the skeleton likely to be absent, but those related to the alterations in the blood are often vague and not diagnostic.

*Diagnosis.*—As with any malady presenting difficulties in diagnosis, it is most important to consider seriously the possibility of hyperparathyroidism in any case in which the symptoms are at all compatible with it. At the present stage of knowledge of this disease, it appears profitable to consider the possibility of hyperparathyroidism carefully in the following cases: (1) all cases of renal stones, (2) all cases in which there is roentgenographic evidence of generalized demineralization of bone, (3) all cases of cysts or tumors of bone and (4) all cases in which there are symptoms referable to the skeleton. In addition, primary hyperparathyroidism deserves serious consideration in cases of urinary insufficiency, in cases of serious muscular weakness and fatigue, and particularly in all cases of polyuria and polydipsia.

Cases in which there are symptoms that are referable to the skeletal system pose few problems excepting in instances in which serious renal insufficiency is also present. Once the attention of the physician is called to the skeleton, the diagnosis of hyperparathyroidism rests upon the demonstration of a specific generalized and diffuse fibrocystic affection of bone accompanied by characteristic chemical changes in the blood and urine.

At the present time, it is not possible to state with accuracy what proportion of patients with renal calculi will prove on careful study to have hyperparathyroidism. Cope<sup>24</sup> stated that between 10 and 15 per cent of patients with renal stones who were investigated personally by himself or Albright eventually were found to have the disease. Since it may be that such patients are unavoidably a somewhat selected group the actual incidence may be less than this figure, but there is no doubt that a significant proportion of patients with renal stones

have hyperparathyroidism. The nature of renal involvement or the duration of symptoms cannot provide a safe guide. Although a number of patients in our series had multiple or bilateral renal stones, and often had had renal colic for many years, one patient (case 34) who had severe hyperparathyroidism due to parathyroid adenoma had had

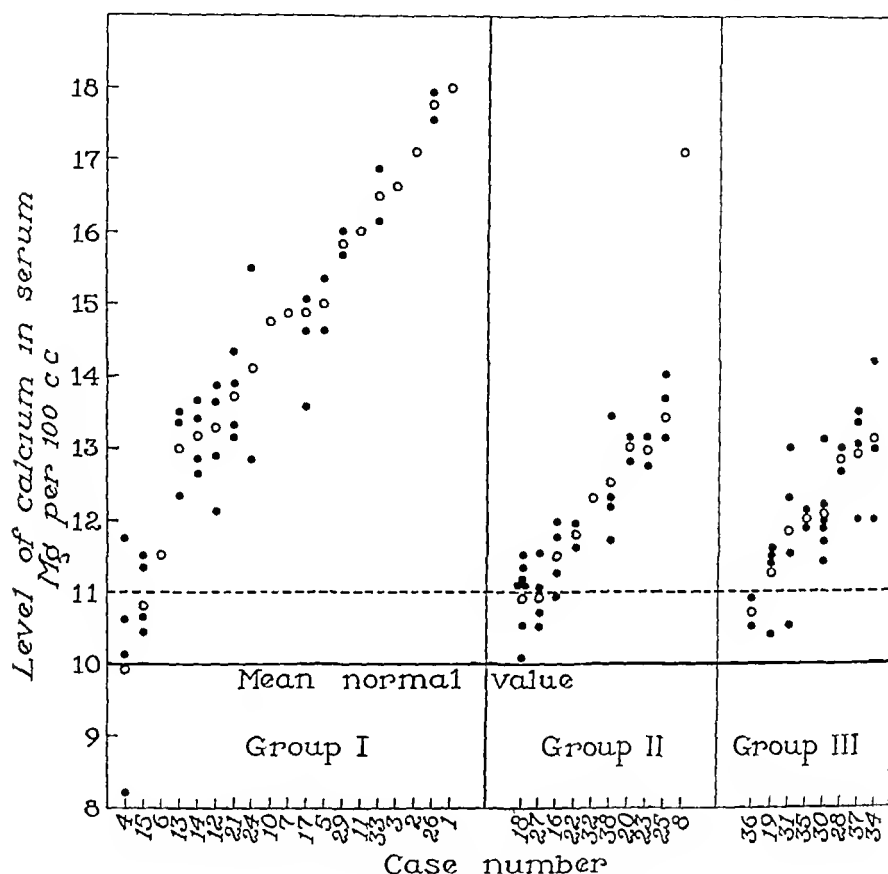


Fig 154—Range of values of serum calcium in thirty-seven cases of proved hyperparathyroidism. The cases are divided into three groups, as follows: Group 1, hyperparathyroidism with classic osteitis fibrosa cystica; group 2, hyperparathyroidism with demineralization or with minimal involvement of bone; group 3, hyperparathyroidism without disease of bone. Within each group the cases are arranged in order of average calcium values. Individual dots in each vertical line represent different determinations of serum calcium in a particular case; the white circles indicate the mean value of serum calcium in that case.

a single renal colic four months previously. In another case (case 22), the only symptom was a single attack of colic which had occurred twelve days previously.

The essential alterations common to all types of primary hyperparathyroidism are hypercalcemia, hypophosphatemia, hypercalciuria and hyperphosphaturia.

**Hypercalcemia**—The accepted normal value for total serum calcium is 100 mg per 100 c.c., plus or minus 10 mg. The value for total serum calcium is characteristically increased in cases of hyperparathyroidism, but in many instances it may be scarcely above the range of normal values. Figure 154 shows the values for the serum calcium in thirty-seven cases in which a parathyroid tumor was found at operation at the Clinic. In five, or 14 per cent, of the cases, the average value was less than 11 mg per 100 c.c. In eight, or 22 per cent, of the

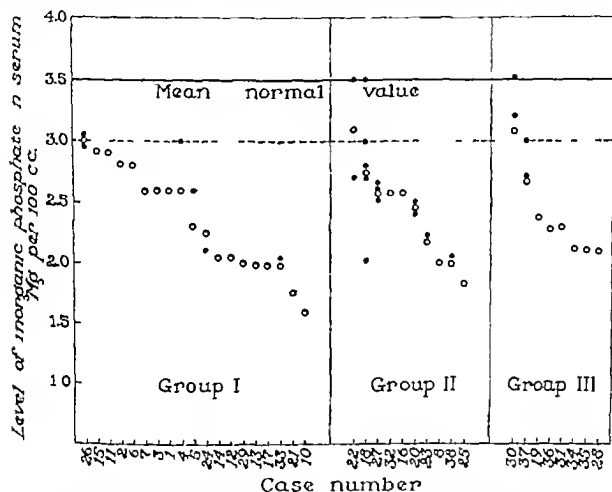


Fig 155—Range of values of inorganic serum phosphorus in thirty-seven cases of proved hyperparathyroidism. The cases are divided into groups as in figure 154 and arranged in order of average values for phosphorus.

cases, the value was less than 11 mg per 100 c.c. on at least one occasion.

The value for the total serum calcium and, consequently, its diagnostic significance are dependent on the value for the total protein in the serum. The calcium in the serum consists of two principal fractions (1) ionic calcium and (2) calcium proteinate, which is a combination of calcium and serum protein. The value for the calcium proteinate varies with the concentration of serum protein and is not affected primarily by the parathyroid hormone. The value for the ionic calcium is affected specifically by the parathyroid hormone. In cases in which the concentration of serum protein is low, the value for the ionic calcium actually may be increased although the value for the



total serum calcium is normal. Unfortunately, the values for the separate fractions of serum calcium cannot be determined directly but, if the values for the total serum calcium and the total serum protein are determined, the values for the separate fractions of serum calcium can be obtained by means of a nomogram devised by McLean and Hastings<sup>34, 35</sup>

Determination of the concentration of the serum protein also is of value in distinguishing hyperparathyroidism from such diseases as multiple myeloma and Boeck's sarcoid, in which the concentration of serum calcium is increased owing to an increased concentration of serum protein

*Hypophosphatemia*—The accepted normal value for inorganic phosphorus in the serum is 3.5 mg per 100 c c, plus or minus 0.5 mg. The value for inorganic phosphorus is significantly lowered in cases of hyperparathyroidism and this change is more constantly present than is hypercalcemia.<sup>6</sup> Figure 155 shows the values for the inorganic phosphorus in the serum in the thirty-seven cases of parathyroid tumor. In three, or 8 per cent, of the cases, the average values were within the normal range. In eight, or 22 per cent, of the cases, the value was within the normal range on at least one occasion. In cases in which the diagnosis is questionable, the values for the calcium and inorganic phosphorus in the serum should be determined repeatedly in order to learn the significance of minimal changes which often are encountered.

*Hypercalciuria*—Sulkowitch has devised a test<sup>15</sup> which furnishes a rough estimate of the amount of calcium excreted in the urine. The test is performed in the following manner: Five cubic centimeters of an oxalate buffer mixture\* is added to an equal amount of urine that is acid to litmus paper. If the reaction is not acid, the urine should be acidified with a 50 per cent solution of acetic acid. The test tube is inverted and shaken, and the degree of turbidity produced by the precipitation of calcium oxalate is classified as grade 1 to 4. The urine of healthy persons who are receiving a diet that contains a normal amount of calcium will show a slight cloudiness (grade 1) whereas the urine of patients with hyperparathyroidism will show a greater degree of turbidity (grade 2 to 4). Unfortunately, if the urine of normal persons is concentrated or they have ingested excessive quantities of calcium (that is milk) it often will show a grade 2 or 3 response. It is important to eliminate dairy products and nuts from the diet for a day or two preceding the test.

Many patients with hyperparathyroidism have polyuria. Since the Sulkowitch test measures only the concentration of calcium, the large

\* The composition of the oxalate buffer mixture is as follows:

Oxalic acid	2.5 gm
Ammonium oxalate	2.5 gm
Glacial acetic acid	5 c c
Distilled water to make	150 c c

volume of urine resulting from polyuria may lead to a negative result when hypercalcinuria actually is present, therefore, the specific gravity must be taken into account.

The Sulkowitch test is useful, therefore, only as a rough guide. A negative result will often rule out hyperparathyroidism if the test is done on a concentrated specimen of urine. A positive result suggests but does not prove, the existence of pathologic hypercalcinuria. In

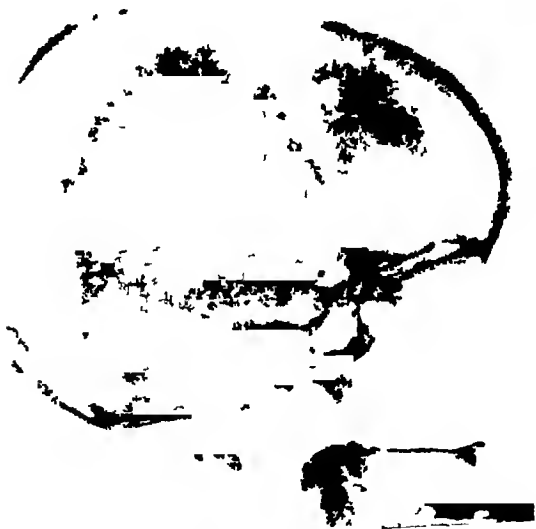


Fig. 156.—Roentgenologic appearance of the skull in case of hyperparathyroidism with classic disease of bone. There is diffuse miliary osteoporosis of the skull with thinning and obliteration of the tables

most instances, therefore, I prefer to rely upon quantitative determination of the excretion of calcium in a specimen of urine collected over a period of twenty-four hours. A normal individual on an average diet may excrete 10 to 100 mg. of calcium daily, a person who drinks milk may excrete as much as 200 mg., while patients with hyperparathyroidism will generally excrete considerably more than 200 mg. of calcium daily. If possible it is preferable to determine the excretion of calcium while the patient is on a diet in which the intake of calcium is accurately measured. Such a diet has been described by Bauer and

Aub<sup>17</sup> The average excretion of calcium by most normal individuals who receive this diet is less than 100 mg a day. An excretion of more than 150 mg a day is considered highly suspicious by Albright, and values exceeding 200 mg a day are regarded as definitely pathologic. Hypercalciuria is not peculiar to hyperparathyroidism, however, as it may occur in other conditions associated with rapid demineralization of bone.

*Roentgenologic Appearance of Lesions of Bone*—In cases in which the skeletal changes are minimal, the only abnormal roentgenologic finding is a mild diffuse miliary osteoporosis of the skull. In cases in



Fig 157—Roentgenologic appearance of the hand in case of hyperparathyroidism with classic bone disease. Generalized demineralization, coarsening of the trabeculae and subcortical absorption may be seen.

which the process is more advanced, there may be evidence of mild generalized demineralization, and subcortical resorption, most conspicuous in the extremities. More marked changes include fibrocystic disease, coarsening and widening of the trabeculae, thinning of cortical bone associated with generalized rarefaction of all bony structures, and the appearance of radiolucent areas in the shafts of long bones, the ribs and even the skull. The presence of large cysts and tumors may make the roentgenographic appearance of the skeleton most bizarre. The most important diagnostic criterion is that when pronounced changes are present in bone the entire skeleton is diffusely and visibly

involved. There is no normal bone, and the demonstration of normal bone in such cases rules out the presence of hyperparathyroidism.

The bony changes in hyperparathyroidism have a predilection for the skull (fig 156), the long bones and particularly the fingers (fig 157) and the ribs. Generalized osteoporosis or atrophy of bone, which also affects the entire skeleton, first affects the spinal column and is generally most pronounced in the vertebrae.<sup>5</sup> Osteitis deformans



Fig 158—Appearance of the dental roentgenograms in case of hyperparathyroidism with disease of bone. The two upper roentgenograms were made a year before symptoms attributable to hyperparathyroidism first appeared. The appearance of the teeth is essentially normal. The lower pair of roentgenograms were made of the same teeth three years after symptoms of hyperparathyroidism appeared. In addition to demineralization the most obvious change is the disappearance of the thin layer of cortex or lamina dura which invests the root of each tooth. It is to be noted that no change has occurred in the density of the teeth themselves.

(Paget's disease), Albright's syndrome, xanthomatosis osseum and solitary tumors of bone are focal, not diffuse, diseases of bone.

Albright<sup>6</sup> and his colleagues have emphasized the usefulness of dental roentgenograms in the diagnosis of osteitis fibrosa cystica. The lamina dura, a fine layer of cortex surrounding the root of each tooth, tends to disappear in hyperparathyroidism (fig 158). It also may be absent in osteomalacia but usually persists in senile osteoporosis. Demineralization of the jaws with derangement of the bony structure is

also characteristic and may conceivably be evident as an earlier stage than similar changes elsewhere in the skeleton

*Significance of Alkaline Serum Phosphatase*—The determination of the concentration of alkaline phosphatase in the serum is of little value in the diagnosis of hyperparathyroidism. Alkaline serum phosphatase is apparently derived from osteoblastic tissue, in any event, an increase in alkaline phosphatase is nearly always indicative of accelerated osteoblastic activity. The concentration of alkaline serum phosphatase is a measure of disease of bone, not of parathyroid disease. In cases of osteitis fibrosa cystica, the value for the serum phosphatase usually is increased. In cases of hyperparathyroidism in which involvement of bone is minimal or absent, the value for the serum phosphatase is normal (2 to 4 Bodansky units)

*Diagnostic Criteria in Cases in Which Hyperparathyroidism Is Complicated by Renal Insufficiency*—When renal insufficiency occurs as a consequence of primary hyperparathyroidism, it tends to obscure the characteristic chemical alterations of blood and urine. The concentration of inorganic phosphorus in the serum may be normal or increased and the degree of hypercalcemia tends to be less marked than it is in cases in which renal insufficiency is not present. Albright clearly demonstrated this in a case in which data were obtained before and after a serious degree of urinary insufficiency had developed<sup>8</sup>

The excretion of calcium and phosphorus may likewise be reduced to normal proportions. This was illustrated in one case (case 15) in our series

The patient was a woman, forty-five years of age, who had uncinat fits and very severe osteitis fibrosa cystica. As a result, innumerable pathologic fractures, many of them in bizarre sites, had occurred. Although symptoms of hyperparathyroidism had been present for only three years, she had a severe degree of renal insufficiency. The urea clearance was 12 c c per minute and the concentration of urea in the blood averaged 60 mg per 100 c c. Notwithstanding the extent of the involvement of bone, the average concentration of total calcium in serum was only 11.5 mg per 100 c c and the average concentration of inorganic phosphorus was 3.0 mg per 100 c c of serum. The excretion of calcium in the urine averaged 35 mg per day. Excision of a parathyroid tumor effected a significant shift in the concentration of calcium and of phosphorus in the serum but apparently did not alter the renal disease.

The accurate diagnosis of mild hyperparathyroidism without disease of bone or with mild disease of bone remains exceedingly difficult. In considering the diagnosis in such instances, Albright stated, "If the serum calcium level itself is not sufficiently high to strongly suggest the disease, one can still be led to the right diagnosis if the serum phosphorus is persistently low, or if the calcium excretion is increased in the urine, or if the clinical picture fits the disease and no other disease. In this group, furthermore, it is important to do repeated determinations as the values fluctuate from the normal range into the definitely hyperparathyroid range"<sup>6</sup>

## DIFFERENTIAL DIAGNOSIS

The differential diagnosis of hyperparathyroidism consists, first in distinguishing it from other conditions producing hypercalcemia and second, in distinguishing it from other diseases affecting the skeleton in a similar manner. Hypercalcemia occurs in hypervitaminosis D, in multiple myeloma, in some cases of metastatic tumors and occasionally in rickets. Lesions of bone which must be distinguished from primary osteitis fibrosa cystica occur in secondary hyperparathyroidism, osteitis deformans (Paget's disease), osteitis fibrosa cystica disseminata (Albright's syndrome), osteomalacia, multiple myeloma, Boeck's sarcoid, generalized osteoporosis and metastatic tumors.

**Secondary Hyperparathyroidism**—Hyperplasia of the parathyroid glands, with apparent compensatory increase in parathyroid function, is encountered in chronic renal insufficiency, rickets, osteomalacia, multiple myeloma, and in some cases of carcinomatosis.<sup>43</sup>

Secondary hyperparathyroidism occurring in consequence of renal insufficiency is believed to be the cause of renal rickets in children<sup>11, 42, 44, 45</sup> and of renal osteitis fibrosa cystica or renal osteodystrophy in adults.<sup>20, 43, 44</sup> It has been suggested as the cause of the generalized demineralization encountered in multiple myeloma and metastatic tumors of bone.

Secondary hyperparathyroidism is therefore of importance in differential diagnosis because it may produce demineralization of bone or osteitis fibrosa cystica in primary renal disease and it may produce hypercalcemia and diffuse demineralization in other diseases of bone. In both circumstances, it may at times pose an exceedingly difficult diagnostic problem.

It is very difficult to distinguish primary hyperparathyroidism with osteitis fibrosa cystica and secondary urinary insufficiency from primary renal disease with accompanying secondary hyperparathyroidism and renal osteitis fibrosa cystica. The differential diagnosis is more than academic, for, in the case of primary hyperparathyroidism, removal of an offending parathyroid tumor may prolong life, whereas, it is not unlikely that, in primary renal disease with secondary hyperparathyroidism, parathyroidectomy may shorten life.

Renal osteitis fibrosa cystica or renal rickets is usually accompanied by a marked increase of concentration of inorganic phosphorus in the serum, often to 8 or 10 mg. per 100 c.c. The concentration of calcium in the serum may be normal or slightly increased. The concentration of serum alkaline phosphatase is usually increased. The urinary insufficiency is usually of marked severity and long standing. In many instances, the correct diagnosis will be expedited by a clear-cut history of glomerulonephritis or of polycystic kidneys. There is usually a chronic acidosis with reduction of plasma bicarbonate owing to loss of fixed base.<sup>4</sup> An antecedent history of renal disease, severe acidosis, a high value for inorganic phosphorus in the serum and a normal con-

centration of serum calcium may make the differential diagnosis simple in a given instance but one can imagine circumstances in which it might prove impossible to distinguish the two conditions. In adults, the roentgenologic appearance of the bones may be indistinguishable in the two conditions. In children, in addition to fibrocystic changes, there are broad irregular epiphyseal disks similar to those seen in true rickets<sup>48</sup>

Some idea of the complicated relationships which may occur may be obtained from a most unusual case reported with postmortem findings by Downs and Scott<sup>27</sup>. The patient, who died of urinary insufficiency, was found to have a parathyroid adenoma, hyperplasia of all non-adenomatous parathyroid tissue, demineralization of the skeleton and nephrocalcinosis. The alterations in the chemistry of the blood were suggestive of secondary hyperparathyroidism. The authors made the reasonable suggestion that the patient initially had primary hyperparathyroidism resulting from the hyperfunctioning parathyroid adenoma. They assumed that this induced nephrocalcinosis, with subsequent renal failure which led to the development of secondary hyperplasia of the nonadenomatous parathyroid tissue and secondary hyperparathyroidism superimposed on the primary disease<sup>1</sup>.

**Other Diseases of Bone**—Serious diagnostic difficulty occasionally may be encountered in cases of multiple myeloma, Boeck's sarcoid and rarely in cases of metastatic carcinoma of bone. In these conditions, the concentration of calcium sometimes may be increased. The concentration of inorganic serum phosphorus in these conditions is generally normal or increased. In multiple myeloma and in Boeck's sarcoid, the hypercalcemia is often, but not always, accounted for by the degree of hyperproteinemia. Biopsy, aspiration of bone marrow and the demonstration of Bence-Jones protein in the urine are often of great assistance.

In generalized osteoporosis, or primary atrophy of bone, demineralization is apparently related to failure of osteoblastic activity rather than to increased absorption of bone. The roentgenoscopic appearance of the skeleton differs markedly from that in osteitis fibrosa cystica. The process is generally most marked in the spinal column and pelvis and less marked in the skull and extremities, the reverse of the distribution generally encountered in hyperparathyroidism. The concentrations of calcium, inorganic phosphorus and alkaline phosphatase in the serum are normal. Apparently similar osteoporosis occurs after the menopause, in association with exophthalmic goiter and with Cushing's syndrome.

Osteitis deformans (Paget's disease) and atypical forms of Albright's syndrome<sup>9, 30, 33</sup> are focal, not diffuse, diseases of bone. Careful scrutiny of the skeleton usually discloses some areas of normal bone, such a finding effectively rules out the presence of hyperparathyroidism. The concentration of alkaline phosphatase in the serum may be in-

creased (at times it is extremely high in osteitis deformans), but the values for calcium and inorganic phosphorus are usually normal and the roentgenologic appearance of the lesions themselves is often diagnostic.

**Hypervitaminosis D**—Hypervitaminosis D may simulate almost exactly the changes in the blood and urine in hyperparathyroidism and the symptoms which result from such changes. The advent of extremely potent preparations of this substance in recent years has made this an important diagnostic consideration. A patient giving a history of having taken vitamin D in large amounts should be observed for many weeks in order to allow the effects of the vitamin to dissipate before any significance is attached to hypercalcemia and related findings.

#### TREATMENT

The treatment of primary hyperparathyroidism is surgical. Roentgen therapy has in general proved unsatisfactory,<sup>25</sup> although a few favorable reports of its use have appeared.<sup>12 13 41</sup>

There is no effective medical treatment. The administration of calcium in large amounts will produce a positive calcium balance and improvement in the skeletal lesions, but at very great risk of irreparable damage to the kidneys.<sup>6</sup> Calcium is, therefore, definitely contraindicated in cases of hyperparathyroidism. The kidneys may best be spared by a diet low in calcium, which of course may lead to further depletion of the skeleton. Nevertheless, if any delay is necessary between the time of diagnosis and surgical ablation of the lesion, a diet low in calcium and containing liberal amounts of fluid is the treatment of choice.

Patients with severe disease of bone and particularly those with a high concentration of serum phosphatase may show severe and intractable tetany postoperatively for several weeks. We have nevertheless preferred total extirpation of the tumor to subtotal removal, as recommended by Cope.<sup>22</sup> Patients with minimal disease of bone or with no involvement of bone seldom have tetany postoperatively.

#### REFERENCES

- 1 Albright, Fuller. The parathyroids—physiology and therapeutics. *J.A.M.A.* 117:527-533 (Aug 16) 1941
- 2 Albright, Fuller and Bloomberg Esther. Hyperparathyroidism and renal disease with a note as to the formation of calcium casts in this disease. *Tr Am. A. Genito-Urin. Surgeons* 27 195-202 (May 15) 1934
- 3 Albright, Fuller and J. C. and Bauer Walter. Hyperparathyroidism a common and polymorphic condition as illustrated by seventeen proved cases from one clinic. *J.A.M.A.* 102 1276-1286 (Apr 21) 1934
- 4 Albright, Fuller, Drake, T. G. and Sulkowitch H. W. Renal osteitis fibrosa cystica: report of a case with discussion of metabolic aspects. *Bull. Johns Hopkins Hosp* 60 377-399 1937
- 5 Albright, Fuller, Smith Patricia H. and Richardson Anna M. Post menopausal osteoporosis its clinical features. *J.A.M.A.* 116 2465-2474 (May 31) 1941



- 6 Albright, Fuller, Sulkowitch, H W and Bloomberg, Esther Further experience in the diagnosis of hyperparathyroidism, including a discussion of cases with a minimal degree of hyperparathyroidism *Am J M Sc* 193 800-812 (June) 1937
- 7 Albright, Fuller, Sulkowitch, H W and Bloomberg, Esther Hyperparathyroidism due to idiopathic hypertrophy (hyperplasia?) of parathyroid tissue, follow-up report of six cases *Arch Int Med* 62 199-215 (Aug) 1938
- 8 Albright, Fuller, Baird, P C, Cope, Oliver and Bloomberg, Esther Studies on the physiology of the parathyroid glands IV Renal complications of hyperparathyroidism *Am J M Sc* 187 49-65 (Jan) 1934
- 9 Albright, Fuller, Butler, A M, Hampton, A O and Smith, Patricia Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females *New England J Med* 216 727-746 (Apr 29) 1937
- 10 Alexander, H B, Kepler, E. J., Pemberton, J deJ and Broders, A C Functional parathyroid tumors and hyperparathyroidism, clinical and pathologic considerations *Am J Surg* 65 157-188 (Aug) 1944
- 11 Andersen, Dorothy H and Schlesinger, E. R Renal hyperparathyroidism with calcification of arteries in infancy *Am J Dis Child* 63 102-125 (Jan) 1942
- 12 Andre, H M, Schnoor, E. W and Van Solkema, Arthur Hyperparathyroidism with osteitis fibrosa cystica, report of a case *J Michigan M Soc* 42 195-197 (Mar) 1943
- 13 Askanazy, M Quoted by Snapper, I Medical clinics on bone diseases a text and atlas New York, Interscience Publishers, Inc, 1943, p 74
- 14 Baker, B M, Jr and Howard, J E Adenoma of parathyroid with renal insufficiency *Bull Johns Hopkins Hosp* 59 251-261, 1936
- 15 Barney, J D and Sulkowitch, H W Progress in the management of urinary calculi *J Urol* 37 746-762 (June) 1937
- 16 Barr, D P, Bulger, H A and Dixon, H H Hyperparathyroidism *J A M A* 92 951-952 (Mar 23) 1929
- 17 Bauer, Walter and Aub, J C Studies of inorganic salt metabolism I The ward routine and methods *J Am Dietet. A* 3 106-115 (Sept.) 1927
- 18 Bauer, Walter, Albright, Fuller and Aub, J C A case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of the parathyroid bodies Metabolic study II *J Clin Investigation* 8 229-248 (Feb) 1930
- 19 Castleman, Benjamin and Mallory, T B The pathology of the parathyroid gland in hyperparathyroidism, a study of 25 cases *Am J Path* 11 1-72 (Jan) 1935
- 20 Castleman, Benjamin and Mallory, T B Parathyroid hyperplasia in chronic renal insufficiency *Am J Path* 13 553-574 (July) 1937
- 21 Churchill, E. D The operative treatment of hyperparathyroidism *Ann Surg* 100 606-610 (Oct) 1934
- 22 Cope, Oliver The surgery of subtotal parathyroidectomy *New England J Med* 213 470-474 (Sept 5) 1935
- 23 Cope, Oliver Surgery of hyperparathyroidism the occurrence of parathyroids in the anterior mediastinum and the division of the operation into two stages *Ann Surg* 114 706-733 (Oct) 1941
- 24 Cope, Oliver Hyperparathyroidism, sixty-seven cases in ten years *J Missouri M A* 39 273-278 (Sept) 1942
- 25 Cope, Oliver Hyperparathyroidism the significance of generalized hyperplasia, report of the seventh case *Clinics* 1 1168-1178 (Feb) 1943
- 26 Curtis, L E. and Feller, A E. Hyperparathyroidism with calcinosis and secondary to renal disease, report of a probable case *Ann Int Med* 17 1005-1014 (Dec) 1942

- 27 Downs, R. S. and Scott, Virgil Hyperparathyroidism with adenoma causing renal failure and secondary hyperparathyroidism report of a case *Arch Int. Med* 67:658-664 (Mar) 1941
- 28 Erdheim, J Ueber Epithelkörperbefunde bei Osteomalacie. *Sitzungsber. d. k. Akad. d. Wissensch. Math. naturw. Cl. Wien.* 116:311-370 1907
- 29 Gentile, R. J., Skinner H. L. and Ashburn L. L. The parathyroid glands malignant tumor with osteitis fibrosa cystica *Surgery* 10:793-810 (Nov) 1941
- 30 Gorham, L. W., Campbell, E. H., Howard W. P., Donhauser J. L. and Rust, N. H. Albright's syndrome a group of cases characterized by osteitis fibrosa disseminata, areas of pigmentation and a gonadal dysfunction. *Clinics* 1:358-385 (Aug) 1942
- 31 Hannon, R. R., Shorr E., McClellan W. S. and DuBois, E. F. A case of osteitis fibrosa cystica (osteomalacia?) with evidence of hyperactivity of the parathyroid bodies. Metabolic study I *J Clin Investigation* 8:215-227 (Feb) 1930
- 32 Jaffe, H. L. Primary and secondary (renal) hyperparathyroidism. *S Clin North America* 22:621-639 (Apr) 1942
- 33 Lichtenstein, Lois Polyostotic fibrous dysplasia *Arch Surg* 56:874-898 (May) 1918
- 34 McLean F. C. and Hastings, A. B. Clinical estimation and significance of calcium ion concentrations in the blood *Am. J. M. Sc.* 189:601-613 (May) 1935
- 35 McLean F. C. and Hastings, A. B. The state of calcium in the fluids of the body. I The conditions affecting the ionization of calcium *J Biol Chem* 108:285-322 (Jan) 1935
- 36 Mandl, Felix Die Behandlung der lokalisierten und generalisierten Ostitis fibrosa *Wien klin. Wchnschr* 39:1046-1048 (Sept. 9) 1926.
- 37 Mandl, Felix Therapeutischer Versuch bei einem Falle von Ostitis fibrosa generalisata mittels Exstirpation eines Epithelkörperchentumors. *Zentralbl. f. Chir* 53:260-264 (Jan. 30) 1926.
- 38 Mayer, Sidney Jr. Nephrocalcinosis and hypertension following hyperparathyroidism terminal dissecting aneurysm. *Bull. Johns Hopkins Hosp* 68:319-328 1941
- 39 Meyer, K. A. and Ragins, A. B. Carcinoma of the parathyroid gland *Surger* 14:287-295 (Aug) 1943
- 40 von Recklinghausen, F. Quoted by Snapper I. Medical clinics on bone diseases a text and atlas. New York, Interscience Publishers, Inc., 1943 p. 74
- 41 Rubinfeld, Sidney Hyperparathyroidism its treatment with roentgen irradiation. *Am. J. Roentgenol* 46:224-231 (Aug) 1941
- 42 Smyth F. S. and Yeazell, Louise A.. Renal dwarfism, renal rickets and secondary hyperparathyroidism *Clinics* 1:717-736 (Oct) 1942
- 43 Snapper I. Medical clinics on bone diseases, a text and atlas. New York. Interscience Publishers, Inc., 1943 225 pp
- 44 Soffer, L. J. and Cohn, Clarence Primary and secondary hyperparathyroidism *Arch Int. Med* 71:630-649 (May) 1943
- 45 Susman, M. L. and Poppel, M. H. Renal osteitis. *Am. J. Roentgenol* 48:726-731 (Dec) 1942
- 46 Wilder, R. M. Hyperparathyroidism tumor of the parathyroid glands associated with osteitis fibrosa *Endocrinology* 13:231-244 (May-June) 1929

## PROTECTION IN ROENTGENOSCOPY

JOHN F BACON AND EUGENE T LEDDY

GENERALLY speaking, protection in roentgenoscopy concerns the prevention of injury of persons working with or near the radiations coming from the x-ray tube, it includes the use of any and all means by which the intensity of these radiations can be reduced to that of the "tolerance dose" By "tolerance dose" is meant that quantity of radiation which may be received by a person repeatedly or at intervals without bodily injury Actually, the term "tolerance dose" is inaccurate and some other term such as "safe dose" should replace it. The rays against which the roentgenoscopist must protect himself come from both the primary beam of the x-ray and the secondary scattering from objects in the path of the primary beam

The basic ideas of using distance and absorptive shielding for protection against roentgen rays were evolved about the same time that dangers of superficial injury through indiscriminate exposure to the rays became obvious At first, the injuries were thought due to electric effects, ultraviolet rays, platinum particles from the x-ray tube and personal idiosyncrasy, and red silk and thin rubber sheets were suggested as protective measures Roentgen himself probably escaped being hurt because he conducted most of his experiments, which were mainly photographic, with the x-ray tube inside a metal box.

In April, 1898, the Roentgen Society in England began to collect evidence on the harmful effects of the roentgen rays Progress on absorptive shielding was, however, slow and confused for some time and, owing either to carelessness or ignorance, injuries and death continued to result The situation was aggravated during the first World War when many diagnostic sets used by the British Army were relatively primitive and a number of prominent roentgenologists became casualties After this, aroused public opinion started the movement toward the better conditions existing today<sup>7</sup>

In the consideration of present-day protection the men who use roentgenologic equipment and need safeguards must be divided into two distinct groups (1) the well-trained roentgenologist and (2) the relatively untrained general practitioners, surgeons and others who in the course of their practice "do a little x-ray work" Protection is a vastly different problem for each group This was strongly emphasized by Hatchette, who pointed out the much greater risk to the untrained man during operation of roentgenologic apparatus Unfortunately, most of the information, warnings and recommendations are placed before the skilled men—those who need it least—rather than before those most likely to be hurt.

The injuries which may occur as a result of roentgen rays may be



shielding and (3) operating procedures. Of these, the last is considered most significant.

In a study of 135 physicians who came to the Clinic between 1919 and 1935 for advice about or treatment of roentgen ray injury, Riggs and one of us (E T L)<sup>10</sup> found that ninety-one had contracted their injuries during reduction of fractures with the roentgenoscope. Of this number, seventy-eight admitted the use of no protection and eleven began to use lead rubber gloves only after injury had become apparent. Some of these men thought the dermatitis was of an allergic nature, perhaps caused by some soap or disinfecting solution in the operating room. In some instances, after receiving injuries to one hand from overexposure, these men used the other hand, again without protection, and suffered similar injury to it. Injury was recorded both from prolonged exposure at one examination and from cumulative effects of repeated unsafe doses. Of the 135, only eight had had any roentgenologic training, and all these eight had failed to follow the recommended measures of protection until they had been injured. The best protection untrained men can have during their work in reducing fractures under roentgenoscopic control is the presence of a roentgenologist to guide them. If this is not possible, observation of the following rather simple rules will cut the number of injuries markedly.<sup>9</sup>

1 Know the output of the machine and the time it takes the machine in operation to reach an output of roentgen rays which represent the limit of safety to the skin. Calibration of the tube in r per minute is essential.<sup>12</sup>

2 Use an aluminum filter at least 1 mm thick.

3 Determine the lowest intensity of rays which allows satisfactory visualization. The technic may consist of factors such as 55 KV, 3 Ma, an aluminum filter 2 mm thick, and a distance of 16 inches (40.6 cm) between the tube and the top of the table in the reduction of average fractures of the extremities.<sup>13</sup>

4 Be certain of thorough "dark adaptation" of the eyes. This is a common source of failure on the part of men who "do a little x-ray." Not having become sufficiently or at all well adapted they need a considerably greater intensity of beam to see reasonably well. Patience is the secret of success here.

5 Wear lead rubber gloves and manipulate the fragments with the hands outside the beam as much as possible. This is most important. In spite of their clumsiness, bulkiness and general inconvenience, lead rubber gloves should be worn during all stages of roentgenoscopic reduction of fractures. It is obvious that the backs of the fingers and hands are most severely injured during such procedures. The thumbs are protected from the beam by the limb of the patient. This being the case, it is inevitable that at some time during the manipulation the backs of the hands come into the direct beam with little or no protection if gloves are not used.

6 Use roentgenograms instead of the roentgenoscope This is a better method and is a safer and almost as fast a way to check the reduction of fractures The use of fast film with a compact portable machine can produce excellent roentgenograms with practically no loss of time. This is the method used at the Clinic and at some city hospitals where more emergency fracture work is done It is highly satisfactory and is strongly recommended over the use of the roentgenoscope during reduction.

The British X-ray and Radium Protection Committee<sup>2</sup> recently recognized the great potential danger of roentgenoscopy in the reduction of fractures and made official recommendations concerning protection and proper use of the roentgenoscope No such official suggestions have been made by any international board of safety or by any of the roentgenologic societies in this country during the past seven years The United States Army, however, has recently issued an order prohibiting the use of the roentgenoscope in reduction of fractures.

Another procedure which claims its share of victims is the removal of foreign bodies under the roentgenoscope, which usually is done by general practitioners and surgeons Unfortunately, the rays from an x ray tube cause no sensation in the hands to warn when enough exposure has been sustained Thus a fragmented foreign body or one that is particularly difficult to remove may require a period of time beyond the safe limit of irradiation to the operator's hands

Roentgenoscopic examinations of the thorax in tuberculosis surveys cause a few injuries, mostly to unskilled users of the apparatus Avoidance of injury here as in other work depends on recognition of the chance of being hurt and reasonable protection against it.

The use of the roentgenoscope after or during removal of a renal stone is advocated in some places Here again, lead gloves and constant attention to other protective devices and procedures are most important.

Unfortunately the only qualification for the practice of roentgenology seems to be the possession of roentgenologic equipment Those who are trained in the use of radiologic apparatus fully understand its Frankenstein possibilities, but in the hands of untrained or careless men these dangers are overlooked The ratio of roentgenologists to men unskilled in the science who come to the Clinic because of irradiation injuries dramatically attests this fact. Many authors advocate the carrying of dental films by physicians while they are either serving or using irradiation equipment. Comparison of the darkness of the films carried with that of films exposed to known amounts of the rays may be sufficiently tangible and shocking to stop the continuation of overexposure and thus prevent future injury. Modern x-ray machines are as safe and reliable as ever made. The advertising of such equipment may

part for the false sense of security possessed by many "men who do a little x-ray work" Much information is spread concerning the shock-proof nature of the machine, its ease of operation and excellence of performance, but never—or at least seldom—in this advertising can one find warnings about the risks that the physician takes in operating the machine One cannot condemn the manufacturers of the apparatus, however, since they are no more bound to teach physicians how to operate the machines than are automobile manufacturers expected to teach purchasers how to drive

It has been proved beyond question that the risks of injury sustained by the roentgenologic specialist are negligible in contrast to the high risk run by the casual user of roentgenologic equipment The faults in technic by which an inexperienced or careless operator may exceed the limits of safety to himself may be summarized as follows<sup>8</sup> (1) lack of technic of examination, (2) excessive "puttering around", (3) incomplete adaptation of the eyes to darkness, (4) too much current and voltage, (5) insufficient filtration in the roentgenologic apparatus, (6) use of too large fields, (7) placing the bare hand in the field, (8) lack of lead rubber protecting gloves, (9) inattention to the time that the roentgen tube has been in operation and (10) ignorance of the protecting devices advocated by the Safety Committee

Looking at the subject of protection from the point of view of the physician who uses roentgenologic apparatus, two general statements stand out Training, common sense and experience are probably the three most important protective devices with which the operator can fortify himself Carelessness and ignorance are the commonest causes of injury from irradiation Ignorance is inexcusable because the recommendations of the safety committees are so clear and concise that all confusion concerning protection is out of the question Carelessness, however, is a common human fault, but if one keeps in mind the potential danger to himself, to the patient and to the associated personnel, carelessness in protection will cease to be a cause of injury The recommendations of the safety committees should be known by everyone and, being known, should be meticulously observed

#### REFERENCES

- 1 Braestrup, C B X-ray protection in diagnostic roentgenology *Radiology* 38 207-216 (Feb) 1942
- 2 British X-ray and Radium Protection Committee Use of x-rays in the manipulation of fractured limbs *Brit M J* 1:84 (Jan 17) 1942
- 3 Chamberlain, W E Fluoroscopes and fluoroscopy, Carman lecture *Radiology* 38 383-413 (Apr) 1942
- 4 Cilley, E I L, Leddy, E T and Kirklin, B R The dangers of roentgenoscopy and methods of protection against them II Some considerations of the size of the beam used in roentgenoscopic examination *Am J Roentgenol* 32 805-807 (Dec.) 1934

- 5 Gilley, L. I. L., Leddy, E. T. and Kirklin, B. R. The dangers of roentgen oscopy and methods of protection against them III The protective power of the barium filled stomach *Am J Roentgenol* 33:88-92 (Jan) 1935
- 6 Hatchette, S. Radiology versus pseudo-radiology *New Orleans M & S J* 92 295-299 (Dec.) 1939
- 7 Kaye, G. W. C. Story of protection (Stanley Melville memorial lecture) *Radiography* 6:41-60 (Mar) 1940
- 8 Leddy, E. T. The dangers of roentgenoscopy summary and recommendations. (Editorial) *Am J Roentgenol* 38:924-927 (Dec) 1937
- 9 Leddy E. T., Roentgenologic risks sustained by the physician not trained in roentgenology *M CLIN NORTH AMERICA* 25 1011-1017 (July) 1941
- 10 Leddy E. T. and Rigos, F. J. Radiodermatitis among physicians. *Am. J Roentgenol* 45:696-700 (May) 1941
- 11 Leddy E. T., Gilley, L. I. L. and Kirklin B. R. The dangers of roentgen oscopy and methods of protection against them I General review of the problem. *Am. J Roentgenol* 32 360-368 (Sept.) 1934
- 12 Stenstrom, Wilhelm and Vigness, Irwin Scattered radiation and variation of roentgen output of x ray generators in practice. *Minnesota Med* 22 517-520 (Aug) 1939
- 13 Stevenson C. A. and Leddy E. T. Dangers of reducing fractures under roentgenoscope and methods of protection against them *Am J Roentgenol* 37 70-82 (Jan) 1937



## THE IMPORTANCE OF DIAGNOSING CHRONIC SUBDURAL HEMATOMA

PHILIP H HEERSEMA AND JOHN G FREEMAN

SUBDURAL hematoma has long been recognized as a concomitant or sequel of injury of the head. Because the treatment of this condition has resulted in complete recovery in a high percentage of cases, the condition automatically has been allocated too readily to the sphere of the surgeon, and even more specifically to the neurosurgeon, whereas in confusing cases in which there is no history of trauma the condition may not even receive surgical attention unless the internist is particularly alert. Contributions to this subject within the past twenty years have been preponderantly those of surgeons, which tends to create the impression that the diagnosis of subdural hematoma is primarily a surgical one. Actually, in very many cases of subdural hematoma the disease may be sufficiently confused with nonsurgical inflammatory and cerebrovascular syndromes to make surgical consultation seem superfluous. Therefore, it seems that it is fitting that more emphasis be placed on making the diagnostician, that is, the internist and the clinical neurologist, more aware of the importance of consideration of this condition in cases in which there is evidence of progressive neurologic or mental defects without a definite history of trauma. Although a history of trauma may be elicited retrospectively or at least suspected, it becomes particularly important to proceed on the strength of certain signs and symptoms without an enlightening history if one is to obtain best results from treatment, for treatment is relatively simple once the diagnosis is considered and made.

There are various classifications of subdural hematoma. A simple classification includes three main groups, namely, acute subdural hemorrhage (rather than hematoma), subacute subdural hematoma and chronic subdural hematoma. In this classification, subdural hygroma, which is a posttraumatic collection of fluid resulting from a rent in the arachnoid, is listed as a subdivision of chronic subdural hematoma. This paper deals chiefly with chronic subdural hematoma because the diagnosis of this condition is very difficult and of course is the primary factor in management.

Munro reported 310 cases of subdural hematoma and classified the respective lesions in two main groups: (1) acute mixed subdural hematomas and (2) chronic subdural hematomas. The second group was divided into two subgroups, namely, fluid hematomas and solid hematomas. Under the heading of fluid hematomas, the author included the lesions which many authors have designated as hygromas. A mixed subdural hematoma contains both blood and cerebro-

spinal fluid and even may contain macerated cortical tissue. The consistency of the lesion depends on the relative proportion of the components. According to Munro this type of subdural hematoma always is due to a craniocerebral injury. In 194 of the 310 cases, the hematoma was of the acute mixed type. In 184 of the 194 cases the presence of a major injury of the brain was verified at operation or necropsy.

To the best of our knowledge, the present paper is the second formal paper on this subject that has appeared in the *Medical Clinics of North America*, the first being that of Lord, however. Holmes and Brock each have reported a case of subdural hematoma in this publication. A number of excellent articles on the subject have appeared in the *Surgical Clinics of North America*.

In 1927, Lord reported an interesting case of spontaneous hematoma in which the correct diagnosis was not made until necropsy was performed. The patient was carefully observed and the fact that the correct diagnosis was not made before death is not surprising when one stops to consider that the knowledge about this condition was comparatively meager when this case was observed. If the correct diagnosis had been made before death, operation undoubtedly would have been performed.

Lord gave a report of this case to forty-seven physicians and requested them to study the report and submit a diagnosis. Of the twenty-five who complied with his request, seven made a diagnosis of lethargic encephalitis, six made a diagnosis of some type of syphilis, five made a diagnosis of tumor of the brain and two made a diagnosis of intracranial hemorrhage. In the remaining five instances the diagnosis was cerebellar abscess, abscess of the brain, cerebrospinal meningitis, cerebral thrombosis and myelitis respectively. If a report of a similar case were sent to a group of practicing physicians today a diagnosis of intracranial hemorrhage probably would be made by considerably more than 8 per cent of the recipients and some of them undoubtedly would mention subdural hematoma. It may be assumed, however, that the correct diagnosis would not be made as frequently as it should be. When patients with a chronic subdural hematoma begin to lapse into a state of coma, the condition comprises much more of an emergency than the condition which prevails in the case of the usual space-occupying lesion of the brain. There are few intracranial conditions in which the variation in the state of consciousness can lull one into the false sense of security occasioned by a temporary remission of symptoms in cases of chronic subdural hematoma.

After the possibility of a chronic subdural hematoma has been considered in a particular case and the findings appear to support this possibility, a history of trauma is an important factor but is not essential for diagnosis. The surgical treatment of subdural hematoma has been reasonably well standardized and the results of such treatment are uniformly good.

It is encouraging to note the number of articles on subdural hematoma that have been published within the past twenty years. The literature on this subject is by no means voluminous nor is much to be gained by padding it in the future with reports of large series of cases except to impress physicians with the relatively frequent incidence of this disease and its importance as a clinical entity. However, reports of unusual cases, which enhance one's diagnostic acumen, are obviously valuable. This is exemplified by the two cases reported by McCall and Love. In one of these cases, the history, symptoms and clinical findings were typical. In the other case, however, there was a high degree of choked disk and the only history of trauma was that the patient had received a "ducking" while he had been swimming.

Although there were earlier reports regarding the relationship of the meninges to hemorrhage, it was Virchow in 1857 who first gave a clear histologic description of the reaction of the dura to hemorrhage and it was he who coined the term "pachymeningitis interna hemorrhagica." He entertained the idea that in certain cases the dura became chronically inflamed. He termed this inflammation "pachymeningitis interna chronica." He mentioned that it occurred among insane patients, but he failed to recognize that insane patients were particularly liable to injury. It was his opinion that an inflammatory process was responsible for the primary formation of a membrane which laid the foundation for oozing hemorrhage by reason of capillary growth into the membrane and a susceptibility of the capillaries to rupture. His opinion prevailed for many years and it was not until 1914 that Trotter advanced the idea that trauma easily could cause a rupture of the veins which bridged the space between the pia mater and the cerebral sinuses since these veins were relatively susceptible to rupture by reason of their sharp angulation and rigid fixation in relation to the longitudinal sinus. It was his opinion that even minor traumatic forces exerted in the proper direction could cause a hemorrhage and that the enclosing membrane subsequently would be derived from the organization of the outer layer of the clot. He was the first to emphasize the increased frequency of trauma among alcoholic and insane patients, in whom it was recognized that there was a higher incidence of subdural hematoma than in the average population. From the diagnostic standpoint, one of the most important contributions made by Trotter was his emphasis of the variation of the state of consciousness, which is of value in distinguishing subdural hematoma from tumor of the brain.

It might be said that the diagnosis of subdural hematoma reached its maturity in America with Putnam and Cushing's classic article which appeared in 1925. In this article, the etiologic importance of trauma was stressed, the pathologic and clinical aspects were considered and the operative treatment was reviewed. In 1932, Gardner advanced a plausible explanation of the latent interval in cases of chronic

subdural hematoma. This explanation was supported by experimental evidence. He expressed the opinion that the increase in size of the hematoma and the consequent compression of the cranial contents were due to an osmotic process. It was reasoned that the degenerative products of the hematoma, which contain a large amount of protein, served to draw from the surrounding cerebrospinal fluid, which contains less protein, to enlarge the encysted hematoma. In general, this complemented Trotter's theory that cerebral compression was due to direct bleeding and cerebral compensation.

In 1932, Fleming and Jones reported a series of eight cases and advocated simple drainage by trephination. This was a great advance in the treatment of fluid or semifluid hematomas since it previously had been considered proper to remove a goodly part of the membrane entrapping the clot. In one case, the hematoma was organized and had to be removed surgically. In the remaining seven cases, the contents of the hematoma were removed by irrigation. In most of these cases there was an immediate return of the intellectual and mental function to normal.

#### ETIOLOGY AND PATHOGENESIS

As we have stated previously, the relation of trauma to chronic subdural hematoma is well established. However, the mechanism of the actual formation of the clot and the cause of the latent period are not so generally agreed upon. The majority of physicians probably agree with Gardner that the increase in the size of the hematoma is due to osmosis. This, incidentally, may also explain the variation in the state of consciousness on the basis of some fluctuation of the volume of the fluid content of the encapsulated hematoma buffered by the compensatory powers of the brain to adjust itself to an acute change in pressure. It is rather well accepted now that both the spontaneous as well as the traumatic type of chronic hematoma may occur, although there are some champions of the role of trauma who can always introduce the irrefutable argument that a traumatic force so mild as to have been completely unnoticed may have been instrumental in the induction of the hemorrhage. On the other hand, however, those who deprecate the high incidence of trauma in cases of subdural hematoma are not willing to subscribe fully to Virchow's idea that pachymeningitis interna chronica precedes the occurrence of chronic subdural hematoma. To sum up the current belief, we would say that the traumatic factor should be considered as one of first importance, that the delay in symptoms represents a partial liquefaction of the encapsulated clot, after which osmosis increases the size of the clot by reason of a higher protein content of the fluid within the capsule as compared with that of the surrounding fluid. The most likely veins whose rupture could produce this hemorrhage are those which bridge the subdural space and rupture at the point of their attachment to the dura on entering into the superior longitudinal sinus. By reason of their position, their

exposure, and the angle of their attachment to the sinus, they are more susceptible to trauma than other vessels of the brain or meninges. Likewise, this may be a reason why so-called spontaneous subdural hematoma also occurs in these sites since these veins are subjected to some type of blood dyscrasia or surrounding inflammatory reaction as a part of general vascular affection and may be rendered so susceptible that activity considered to be entirely normal might be sufficient to result in spontaneous hemorrhage.

The limiting membrane of a subdural hematoma still is a controversial subject. Certain neurosurgeons have cast doubt on existence of an intradural hematoma by stating that they never have seen one. This presupposes that the limiting membrane is the product of the clot and that fibroblasts grow out from the leukocytes or from the neighboring meninges and produce the limiting membrane. This fits in much more closely with the theory that trauma always is an etiologic factor. The adherents of the theory that the limiting membrane of the clot is actually a part of the dura which is split off and that the hematoma is actually intradural also offer some very sound arguments. Baker, for instance, in adhering to this intradural theory, raised the following question: If the clot is subdural and the membrane is formed from the dura (that is, after the clot has occurred on the dura), why would the various cells go all the way to the inner or arachnoid surface of the clot and form a membrane rather than produce a gradual progressive organization of the entire clot? Yet, aside from the encapsulating membrane, the dura may be perfectly normal and remain so after evacuation of the clot. In our opinion, the incidence of both traumatic and spontaneous hemorrhage can be more satisfactorily explained on an intradural rather than a subdural basis. However, it is not the purpose of this paper to deal with the academic aspects but rather to emphasize the practical clinical features of this interesting clinical entity.

#### MATERIAL

This paper is based primarily on twenty-five consecutive cases of chronic subdural hematoma that were observed at the Clinic in a period of thirty-five months, that is, between January 1, 1941 and November 30, 1943, inclusive. In all of these cases, the diagnosis was proved by operation or necropsy at the Clinic. In general, this series of cases furnishes a concise picture of our experience with chronic subdural hematoma. This series does not include any case in which the patient was an infant. Subdural hematomas of infants comprise a special field. Their diagnosis and treatment have been summarized very well by Ingraham and Matson. The differential diagnosis of chronic subdural hematoma is the problem of the internist. On the other hand, in cases of acute subdural hematoma (hemorrhage), the surgeon should decide when trephination alone or in combination with ventriculography or encephalography should be performed.

## SYMPTOMS AND SIGNS

The symptoms of chronic subdural hematoma may be divided into three groups (1) those that are due to a general increase in pressure, (2) those that are due to fluctuation in the volume of the contents of the hematoma and (3) those that are due to local pressure on adjacent structures. Headache is the most frequent symptom that is due to an increase in intracranial pressure. Headache occurred in 96 per cent of the cases which form the basis of this report (table 1). This figure is about the same as similar figures in other reports, for example, headache occurred in 93.6 per cent of a series of cases reported by Kunkel and Dandy. In some cases in which the patients were in coma when

TABLE 1—SYMPTOMS IN TWENTY-FIVE CASES OF CHRONIC SUBDURAL HEMATOMA

Symptoms	Cases	
	Number	Per cent
Headache	24	96
Nausea and vomiting	9	36
Dizziness	7	28
Confusion and defective memory	5	20
Excitement	4	16
Drowsiness	3	12
Convulsions	2	8
Numbness	1	4
Coma	10*	40

\* In these cases, the patients were in coma when they were brought to the Clinic.

they were brought to the Clinic, the relatives stated that headache had been the chief symptom. Nausea and vomiting which often are associated with progressive pressure occurred in less than half of the cases in this series. Although dizziness and disturbances of equilibrium do occur, they are of little diagnostic significance. Syncopal attacks are rather rare. Convulsions occurred in only 8 per cent of the cases in this series and the nature of the convulsions did not aid in the localization of the lesions in any of these cases.

It is believed that there is a certain amount of fluctuation in the volume of the hematoma which causes a variation in the intracranial pressure. As a result, a variable state of consciousness occurs. This may

vary from a lapse of memory to aberrations of behavior or frank coma. This change is of great importance in making a diagnosis of chronic subdural hematoma. It is not unusual for a semicomatose state or mental stupor to develop in a few days or even within a few hours. For a number of days preceding this change in the state of consciousness there will be a defect in memory or orientation. The change also may be preceded by headache, drowsiness, vertigo, nausea and vomiting.

TABLE 2—PRINCIPAL PHYSICAL SIGNS AT TIME OF INITIAL EXAMINATION AT THE CLINIC

Physical Signs	Cases	
	Number	Per cent
Slow pulse rate (below 70)	14	56
Choked disk (less than 2 diopters)	9	36
Hyperreflexia, bilateral	8	32
Hyperreflexia, unilateral	1	4
Hemiparesis and spasticity, bilateral	6	24
Hemiparesis and spasticity, unilateral	3	12
Babinski's reflex, bilateral	6	24
Babinski's reflex, unilateral	3	12
Paresis of oculomotor nerve (ptosis of upper eyelid)	5	20
Paresis of oculomotor nerve (limitation of movement of eyeball)	2	8
Paresis of facial nerve	5	20
Unilateral enlargement of pupil (both pupils were homolateral)	2	8
Stiffness of neck	1	4

Symptoms that are due to the pressure of the hematoma on adjacent structures do not occur consistently. Diplopia, ocular palsy, hemiparesis and jacksonian epilepsy usually do not occur until the condition of the patient becomes critical.

In the majority of the cases in which the patients were conscious when they came to the Clinic, the symptoms and signs were of a mild character. If only a cursory examination had been performed, it is entirely possible that, in some cases, treatment might have been di-





between the trauma and the appearance of symptoms, the etiologic role of the trauma should be seriously discounted

There is little relation between the degree of the trauma and the development of a subdural hematoma. In our experience, it seems that a subdural hematoma is more likely to follow a slight injury of the head than it is to follow a serious injury. In this connection, we might add that we wish chiefly to emphasize the diagnosis of chronic subdural hematoma in cases in which there is no history of trauma.

The chief value of examination of the cerebrospinal fluid in cases of chronic subdural hematoma is to rule out the presence of an inflammatory disease. In one case in this series, repeated cytologic and chemical examination of the cerebrospinal fluid disclosed changes that were suggestive of a chronic inflammatory disease but the pressure of the fluid was higher than it is in chronic inflammatory disease and indicated the need for surgical intervention.

In five (20 per cent) of the cases in this series, roentgenographic examination of the skull disclosed that the pineal gland had been displaced to one side. In four of these five cases, this finding was confirmed at operation. The diagnosis may be confirmed by encephalography or ventriculography but neurosurgeons generally are critical of these procedures. Bucy actually suspected that pneumo-encephalography was instrumental in causing a subdural hematoma in one case. Some authors believe that the removal of some cerebrospinal fluid and its replacement with air may interfere with the dynamics of the cerebrospinal fluid sufficient to add to the gravity of the situation in the case of a spatial lesion of the brain.

In half of the cases in this series, electro-encephalography disclosed unilateral delta waves, which aided in localizing the lesion. Rogers said that in his cases of chronic subdural hematoma the electro-encephalogram tended to be of the low potential type but this has not been our experience. In our series of cases, electro-encephalography disclosed generalized delta waves in the affected region but in some cases this finding was too extensive to be of any localizing value. In 38 per cent of our cases, electro-encephalography disclosed generalized delta waves or bilateral delta waves. The extent of the abnormal graph was not unexpected as a hematoma frequently involves an entire hemisphere of the brain. In the remaining 12 per cent of the cases, the electro-encephalograms were normal, which finding must be considered erroneous.

**Differential Diagnosis—*Tumor of the Brain***—In cases of tumor of the frontal lobe, there may be a definite change in personality but this develops gradually and insidiously. In cases of chronic subdural hematoma, irritability, mental confusion and disturbances of the sensorium usually develop abruptly.

In cases of subdural hematoma, the symptoms vary, in cases of tumor of the brain, the severity of the symptoms increases progres-

sively Hemiparesis may occur in both diseases, but in case of subdural hematoma a positive Babinski sign or paresis of the cranial nerves is not likely to occur until evidence of a great increase in intracranial pressure has become manifest. A severe degree of choked disk occurs in cases of tumor of the brain in cases of subdural hematoma the degree of the choked disk rarely is greater than 2 diopters. Headache occurs in both diseases. Although it is an important symptom, it is of little value in localizing the lesion. King reported an interesting case in which the patient insisted that an exploratory craniotomy be performed for so-called posttraumatic headache. The operation disclosed a subdural hygroma.

*Encephalitis*—In cases of chronic subdural hematoma, the presence of drowsiness may cause the disease to be mistaken for encephalitis. In subdural hematoma, drowsiness is likely to be associated with mental dullness in encephalitis, there is no relation between drowsiness and the mental condition of the patient. A diagnosis of encephalitis is made too often in cases of intracranial lesions of obscure origin. Headache, drowsiness, diplopia, restlessness and insomnia are common symptoms of both of these diseases. This error is made because of insufficient regard to the variability of the drowsiness and mental torpor in cases of subdural hematoma. If the encephalitis has become chronic, the number of cells in the cerebrospinal fluid may be increased only slightly and the pressure of the fluid may be within normal limits. If at any time, the pressure of the spinal fluid increases or if there is other evidence of increased intracranial pressure, for example papilledema, a diagnosis of encephalitis should be discounted and serious consideration given to the possibility that a subdural hematoma may be present. In cases of acute encephalitis the temperature usually is increased and one usually encounters a serious disturbance of sleep, abnormal psychomotor activity and cloudiness of the mental status which is more severe than that observed in cases of chronic subdural hematoma.

*Cerebral Thrombosis*—The differential diagnosis of cerebral thrombosis and chronic subdural hematoma is not difficult if one considers that the latter disease may be present. The clinical picture of cerebral thrombosis is rather constant and is familiar to most physicians. The only difficulty encountered in the differential diagnosis of cerebral thrombosis and chronic subdural hematoma occurs in cases in which an attempt is made to explain an unusual type of "cerebral vascular accident." In cases in which the symptoms fluctuate but become more severe progressively, and especially in cases in which there is an acute episode during which the symptoms become more severe, a diagnosis of cerebral thrombosis should not be made unless there is concomitant evidence of acute shock, cardiac disease, palsy or hemiplegia. In cases of deepening coma in which Babinski's sign is positive bilaterally, a spinal puncture should be performed and the pressure of the cerebrospinal fluid should be determined. If the pressure is increased but the

cerebrospinal fluid is otherwise essentially normal, a subdural lesion probably is present

*Syphilis of the Central Nervous System.*—In cases of syphilis of the central nervous system, the diagnosis usually can be made by means of serologic tests.

*Other Lesions of the Brain*—In cases of meningitis and abscess of the brain, there is a febrile reaction and the diagnosis usually is aided by examining the blood and cerebrospinal fluid, in addition to the infectious features of the history

#### COMMENT

Death occurred in three of the cases in our series but none of the deaths could be attributed to operation. In two of the three cases, the patients were not referred to a surgeon. In these three cases, the patients were more than sixty years of age, that is, at the age at which confusing vascular syndromes are likely to occur. In sixteen of the twenty-two cases in which the patients survived, the results were very good. In at least a third of these cases, the physical condition of the patient returned to normal within a month. In three cases, the patients were having occasional attacks of convulsions when the last follow-up data were obtained. One patient had mild hemiparesis and spasticity. Another patient had periods of aphasia but his condition subsequently improved. In one case, a severe anxiety state occurred after operation.

Bilateral hematomas were found in three (12 per cent) of the cases. This incidence of bilateral hematomas is slightly lower than that reported by some authors but it is high enough to warrant consideration in every case of suspected subdural hematoma.

In most cases of chronic subdural hematoma, the patients withstand trephination better than they do encephalography. In cases in which the presence of a subdural hematoma is suspected, trephination, followed by ventriculography if necessary, is superior to the preliminary introduction of air in making a diagnosis.

Special consideration of the diagnosis of chronic subdural hematoma should always be given, especially if the patient is aged, in the suspected case of intracranial lesion in which variations of mental alertness are noted, the neurologic signs are likewise variable, the headache is persistent and the entire course is relatively brief. This also holds true in those cases in which a history of trauma has not been elicited.

#### REFERENCES

- 1 Baker, A. B. Subdural hematoma. *Arch Path* 26:535-559 (Aug.) 1938
- 2 Brock, S. Neurologic clinic. 2 unusual cases of parosmia, unusual case of subdural hematoma, aneurysm of intracranial portion of left internal carotid artery. *M. CLIN. NORTH AMERICA* 13:667-678 (Nov.) 1929
- 3 Bucy, P. C. Subdural hematoma. *Illinois M. J.* 82:300-310 (Oct.) 1942
- 4 Fleming, H. W. and Jones, O. W., Jr. Chronic subdural haematoma, simple drainage as method of treatment, report of 8 cases. *Surg., Gynec. & Obst.* 54:81-87 (Jan.) 1932



## CIRRHOSIS OF THE LIVER PRESENTING THE CLINICAL FEATURES OF XANTHOMATOUS BILIARY CIRRHOSIS, BUT WITH CONFIRMATION AT AUTOPSY

(Follow-up of Case Reported Previously\*)

F W HOFFBAUER, M.D, G T EVANS, MD AND C. J WATSON, MD

IN a series of cases of cirrhosis of the liver discussed by the present authors in the March 1945 issue of the *Medical Clinics of North America*, one case (Case III) was included which presented the clinical manifestations indicative of the diagnosis of xanthomatous biliary cirrhosis. In the interim since this report, this patient has come to autopsy, the findings of which were so instructive that it was believed they should be recorded as a supplement to the previous report. Reference to this report will reveal that this patient exhibited the characteristic hypercholesterolemia together with multiple xanthomas of the tendon sheaths, in addition to which there was chronic jaundice and manifest evidence of cirrhosis of the liver. Liver biopsy revealed a picture of an ordinary portal cirrhosis, and there was no evidence in the biopsy of intrahepatic xanthomas. As Thannhauser has emphasized, however, it is known that in xanthomatous biliary cirrhosis the obstructing xanthoma may be found only in the larger bile ducts. This patient died in coma exhibiting evidence of severe uremia, and with an obvious pericarditis. It was difficult to determine how much of the coma was due to hepatic insufficiency and how much to renal insufficiency. The blood urea nitrogen was 102 mg per 100 cc. Shortly before death the serum bilirubin was 14 mg per 100 cc, the serum cholesterol was 375 mg per 100 cc, the cephalin cholesterol flocculation test remained 4+. The marked pruritus persisted until death.

The important findings at autopsy were as follows: (1) diffuse fibrinous pericarditis, (2) extensive diffuse hobnail type of cirrhosis of the liver, which weighed 1600 gm. The common duct was not dilated, but near the lower end of the duct a gallstone was found as noted in Figure 159. This was dark in color, and was found to consist almost entirely of calcium bilirubinate. Ether extraction failed to reveal any appreciable amount of cholesterol. Sections of the liver revealed an extensive diffuse portal cirrhosis of Laennec type (Fig 160).

The anatomic findings in this case reveal that it is impossible to make the diagnosis of xanthomatous biliary cirrhosis with any degree of certainty, since in this case the blood chemical findings and the presence of xanthomas of the tendon sheaths were entirely characteristic and in fact strongly suggestive of the condition, yet at autopsy no evidence was obtained of xanthomas in the biliary tract. Nor was there any intrahepatic xanthomatous change such as described by Chvostek and believed by him to have been productive of cirrhosis. It is believed that the stone found in the common duct was a secondary phenomenon since, after seven years of jaundice, the common duct might have been expected to be dilated had the stone been the causative factor in the production of cirrhosis. The fact that the stone was largely composed of calcium bilirubinate and relatively little if any cholesterol suggests that it was simply due to inspissation of the bile, secondary to the reduced bile output of the cirrhotic liver.

---

From the Department of Medicine and the Laboratory Service, University of Minnesota Hospital, Minneapolis, Minnesota

\* Hoffbauer, F W, Evans, G T and Watson, C J. Cirrhosis of the Liver With Particular Reference to Correlation of Composite Liver Function Studies with Liver Biopsy. *M CLIN NORTH AMERICA*, 29(2) 363-388 (March) 1945



Fig 159.—Postmortem appearance of common bile duct showing position of pigment stone near ampulla. The upper one-sixth of the stone has been cut off for chemical analysis. Note that the common bile duct, cut open longitudinally is not dilated.



Fig 160.—Photomicrograph of liver postmortem specimen. The ported portal cirrhosis of the Laennec type

## CUMULATIVE INDEX

- ABORTION, early, progesterone in, *Jan*, 264  
 emergency aspects, *July*, 853, 856  
 Abruptio placentae, *July*, 855, 857  
 Abscess, intracranial, emergency treatment, *July*, 895  
   of lung, emergency aspects, *July*, 841  
 Achlorhydria, acid therapy, *March*, 426  
 Actinomycosis, *March*, 338  
 Addison's disease, *July*, 1016  
   desoxycorticosterone acetate in, *March*, 435  
 Adenoma of bronchus, hemoptysis in, *July*, 843  
   parathyroid, *March*, 390-393  
 Adrenal cortex, disturbances, *July*, 1016  
   medulla, disturbances, *July*, 1016  
 Agglutination test for brucellosis, *March*, 353  
 Albumin, human, *March*, 433  
 Albuminocytologic dissociation in acute infectious radiculoneuritis, *Jan*, 1  
 Alcohol injections for facial pain, *Jan*, 77  
 Alcoholism, criminal responsibility and, *Jan*, 212  
 Alloxan in production of diabetes, *March*, 436  
 Aluminum hydroxide in hypoparathyroidism, *March*, 435  
   powder in silicosis, *March*, 437  
 Amebiasis, postwar problem of, *July*, 906  
 Amenorrhea, hormone therapy, *Jan*, 258, 260, 263  
 Amigen, *March*, 433  
 Amino acids, parenteral uses, *March*, 433  
 Aminophylline in asthma in children, *July*, 867  
 Anaphylactoid purpura, *July*, 880  
 Androgen therapy, advances in, *March*, 436  
   in menstrual disorders, *Jan*, 265  
 Anemia, hemolytic, acute acquired, *May*, 695  
   in carcinoma of colon, *July*, 958  
   Lederer's, *May*, 702  
   pernicious, *Jan*, 229  
     clinical types, *Jan*, 230  
     liver therapy, *Jan*, 242  
     posterolateral sclerosis in, management, *Jan*, 245  
   severe, electrocardiogram in, *May*, 608  
   suspension of discarded erythrocytes in, *March*, 432  
 Anemias, macrocytic, *Jan*, 246  
 Anesthesia, general, curare in, *March*, 423  
   local, new agents, *March*, 419  
   surgical, electrocardiogram in, *May*, 614  
 Angina pectoris, anoxemia test, *May*, 616  
   differential diagnosis, *March*, 513  
   testosterone in, *March*, 425  
 Ankle clonus in pyramidal tract lesions, *Jan*, 56  
 Anoxemia test in angina pectoris, *May*, 616  
 Anthrax, penicillin in, *July*, 835  
 Anuria in infants and children, *July*, 874  
 Anxiety, later fate of, *May*, 747  
   neurosis, in combat crews, *May*, 731  
 Aorta, aneurysm, electrocardiograms in, *May*, 605  
   coarctation, electrocardiogram in, *May*, 605, 606  
 Appendicitis, acute, in children, *July*, 879  
   chronic, simulating peptic ulcer, *May*, 629  
 Army Air Forces, rehabilitation in, *May*, 715  
   rheumatic fever in, convalescent care, *May*, 765  
 Army, fatigue and exhaustion states in, *May*, 771  
   reconditioning programs, *May*, 788  
 Arrhythmias, digitalis in, *March*, 531  
   quinidine in, *Jan*, 216  
 Arthritis, physical medicine in, *May*, 790  
   rheumatoid, etiology, environmental factors, *May*, 566  
   neostigmine in, *March*, 423  
 Aspiration biopsy of liver, *March*, 365  
 Aspirin, blood coagulation and, *March*, 430  
 Asthma, bronchial, complications, unusual, *March*, 456  
   military service and, *March*, 455  
   recent advances, *March*, 453  
   treatment, *March*, 458, 461  
   emergency aspects, *July*, 843  
   in children, *July*, 866  
   with heart disease in children, *July*, 871  
 Atelectasis, massive, emergency aspects, *July*, 844  
 Auricular fibrillation, digitalis in, *March*, 532  
   quinidine in, *Jan*, 217  
   flutter, digitalis in, *March*, 532  
   quinidine in, *Jan*, 223  
 Axillary nerve injuries, *Jan*, 23  
 BABINSKI sign in pyramidal tract lesions, *Jan*, 47  
 Bacillary dysentery, postwar problem of, *July*, 905  
 Back strain, *May*, 568

- Barbiturates in war psychoses, *March* 418
- Basophilism, pituitary, *July* 1011
- Bed rest in convalescence, undesirable effects, *May* 720, 748 809
- Behavior Clinic of criminal court, *Jan.* 202
- Benzedrine in prevention of motion sickness, *March* 418
- Berberi, diet in *May* 803
- Biopsy endometrial, *Jan.* 252
- in lymphogranuloma venereum *May* 678
- liver by aspiration *March* 365
- Bladder atony, furmethide in *March* 421
- Blastomycosis, *March* 334
- Blood coagulation, drugs influencing *March*, 430
- loss, acute, electrocardiogram in *May* 613
- vessels, peripheral effect of cigarette smoking in, *July* 949
- Bones, lesions, in hyperparathyroidism *March* 394 396
- Brachial plexus injuries, *Jan.* 19
- Brain tumor in children *July* 892
- Bromsalizol, *March* 419
- Bromsulfalein test of liver function *July*, 976
- Bronchial asthma, recent advances, *March* 453
- Bronchiectasis, emergency aspects, *July* 840
- Broncholithiasis, emergency aspects *July* 842
- Bronchopneumonia in infants and children, *July* 869
- penicillin in, case report, *May* 580
- Bronchus, adenoma of hemoptysis in *July*, 843
- Brucella, *March* 359
- Brucellosis, *March* 343
- penicillin failure in *May* 586
- Buboes, inguinal in lymphogranuloma venereum, *May* 668
- Bubonoli, *May* 669 670
- Burns, infection due to penicillin in *July* 836
- shock in sodium lactate in *March* 438
- CANDIDA albicans infections with *March* 323
- Carbon dioxide in bronchial asthma *March* 459
- Carbuncles penicillin in, *July*, 836
- Carcinoma of colon proximal portion iron deficiency and anemia associated with *July* 958
- of lung, emergency aspects *July* 842
- of prostate, estrogen therapy *March* 435
- of stomach diagnosis *March* 489
- gastroscopy in, *March* 499
- Caruncle of urethra, *July* 1007
- Cataplexy, potassium chloride in *March*, 422
- Catarrh, gastric with peptic ulcer, *May* 628
- Causalgia, *Jan.*, 13
- Cauterization of cervix in chronic cervicitis, *July* 1002
- Cavernostomy in tuberculosis, *March*, 450
- Cavernous sinus thrombosis emergency treatment, *July* 894
- Cedilanid, *March*, 424 529
- Cellulitis penicillin in *May*, 584, *July*, 836
- Cerebral palsies of children, rehabilitation in, *May* 792, 819
- thrombosis in children *July*, 894
- Cervicitis, chronic, *July* 998
- Chaddock's sign in pyramidal tract lesions *Jan* 50
- Chemotherapy in brucellosis, *March* 357
- in lymphogranuloma venereum, *May*, 682
- in tuberculosis, *March* 445, *July*, 918
- in urinary tract infections, *May*, 574, 575
- Children cardiac emergencies in, *July*, 871
- gastro intestinal emergencies in *July* 878
- neurologic emergencies in, *July*, 886
- respiratory tract emergencies in, *July*, 864
- urinary tract emergencies in, *July*, 874
- Cholera postwar problem of, *July* 901
- Cholesterothorax, *March*, 507 510
- Choline in cirrhosis of liver, *March*, 429 484
- Chordotomy for intractable pain *Jan* 98
- Choriomeningitis, lymphocytic, benign *Jan.*, 36
- Chromoblastomycosis, *March*, 336
- Chylothorax *March*, 506 510
- Cigarette smoking effect on heart and peripheral blood vessels, *July*, 949
- Circus movement, *Jan.*, 216
- Cirrhosis of liver correlation of composite liver function study with liver biopsy, *March* 363
- diagnosis, *March*, 480
- dietary treatment *March*, 276 429 484 485 *May* 655
- etiology, *March* 273 479
- lipotropic substances in, *March*, 428 484 *May*, 658
- nutritional deficiencies as basis *May*, 655
- symptoms and signs *March*, 275
- treatment recent advances, *March*, 273, 479
- with clinical features of xanthomatous biliary cirrhosis but with confirmation at biopsy *July*, 1054
- Clawed hand in ulnar nerve injury *Jan* 15



- Clonus in pyramidal tract lesions, *Jan*, 56  
 Coccidioidin, *March*, 334  
 Coccidioidomycosis, *March*, 332  
   postwar problem of, *July*, 907  
 Cold, common, propadrine hydrochloride in, *March*, 420  
 Colic in infants, *July*, 878  
 Colitis, chronic ulcerative, sulfathalidine in, *March*, 427  
 Colon, diverticulitis and diverticulosis clinical study, *May*, 639  
   proximal portion, carcinoma of, iron deficiency and anemia associated with, *July*, 958  
 Coma, diabetic, *July*, 893  
   in children, emergency treatment, *July*, 892  
 Complement fixation test in lymphogranuloma venereum, *May*, 678  
 Convalescence, bed rest in, undesirable effects, *May*, 720, 748, 809  
   in home, rehabilitation problems, *May*, 818  
   in hospital, rehabilitation problems, *May*, 808  
 Convalescent care of rheumatic fever in Army Air Forces, *May*, 765  
   hospital, Army Air Forces, role of, *May*, 721  
   training program, Army Air Forces, *May*, 716  
   ward, need for, *May*, 812  
 Convulsions in children, emergency treatment, *July*, 886  
 Coronary occlusion, quinidine in, *Jan*, 227  
   restriction of activity in, and extent of myocardial infarction, *March*, 405  
   thrombosis, electrocardiograms in, *May*, 598  
   pain of, differential diagnosis, *March*, 513  
 Criminal responsibility, epilepsy and, *Jan*, 212  
   insanity and, *Jan*, 195  
   mental retardation and, *Jan*, 208  
 Croup, *July*, 864  
 Cryptococcosis, *March*, 335  
 Curare, new uses, *March*, 423  
   test for myasthenia gravis, *Jan*, 129  
 Cushing's syndrome, *July*, 1011  
 Cystic disease of lung, emergency aspects, *July*, 845  
 Cystine in liver disease, *March*, 429  
 D-DESOXYEPHEDRINE hydrochloride, *March*, 420  
 Deficiency diseases, rehabilitation problems, *May*, 794  
 Dementia praecox, *Jan*, 148  
 Demerol, *March*, 417  
 Dengue fever, postwar problem of, *July*,  
   Depression in combat crews, *May*, 732  
   in returned soldiers, *May*, 736  
 Dermatitis, acute, emergency aspects, *July*, 833  
 Dermatology, nonsurgical emergencies encountered in, *July*, 833  
 Dermatophytosis, *March*, 323  
   treatment, *March*, 326  
 Desoxycorticosterone acetate in Addison's disease, *March*, 435  
 Diabetes insipidus, *July*, 1009  
   melitus, *July*, 1014  
   globin insulin in, *March*, 436  
 Diabetic coma, *July*, 893  
   electrocardiogram in, *May*, 608  
 Diarrhea, acute, in infants and children, *July*, 882  
 Diasone in tuberculosis, *March*, 447, 448, *July*, 921  
 Dichlorophenarsine hydrochloride in syphilis, *March*, 438  
 Dicoumarol in prevention of embolism and thrombosis, *March*, 430, 431, *July*, 840, 929  
 Dienoestrol, *March*, 435  
 Diet in cirrhosis of liver, *March*, 276, 427, 484, *May*, 655  
   in nutritional deficiencies, *May*, 799-802  
   in peptic ulcer, fundamental importance, in Army hospital, *May*, 706  
   in pernicious anemia, *Jan*, 244  
   in rehabilitation, *May*, 794  
 Digilandin, *March*, 423  
 Digitaline nativelle, *March*, 423  
 Digitalis, blood-clotting and, *March*, 431  
   effects on electrocardiogram, *May*, 609  
   in arrhythmias, *March*, 531  
   in heart failure, *March*, 524  
   preparations and uses, *March*, 423, 524  
 Digitoxin, *March*, 423  
 Digoxin, *March*, 424, 529  
 Dihydrotachysterol in hyperparathyroidism, *March*, 402  
 Dilantin sodium in bronchial asthma, *March*, 459  
 Diphtheria, laryngeal, *July*, 866  
 Diuretics, new, *March*, 424  
 Diverticulitis of colon, *May*, 639  
 Diverticulosis of colon, clinical study, *May*, 639  
 Diverticulum, urethral, *July*, 1008  
 Drop wrist in radial nerve injury, *Jan*, 10  
 Dye excretion tests of liver function, *July*, 976  
 Dysentery, amebic, postwar problem of, *July*, 906  
   bacillary, postwar problem of, *July*, 905  
   sulfasuxidine in, *March*, 426  
   sulfathalidine in, *March*, 426  
 Dysmenorrhea, hormone therapy, *Jan*, 259, 262, 265, 267

- Dyspnea, pulmonary disturbances causing emergency aspects *July* 843
- ECLAMPSIA, *July*, 852
- Ectopic pregnancy ruptured *July* 854 856
- Edema of lung, acute, emergency aspects, *July* 837
- Educational retraining in Army Air Forces, *May* 721
- Electrocardiography uses in medicine *May*, 590
- ventricular gradient in, *March* 464
- Electrodiagnosis in peripheral nerve injuries, *Jan.*, 23
- Electroshock therapy in psychoses with insomnia, *Jan.*, 192
- outpatient, in psychiatric disorders *Jan.*, 165
- Embolism, prevention, dicoumarol in *March*, 430 431, *July* 840 929
- heparin in, *March*, 431 *July* 933
- pulmonary, emergency aspects, *July* 839
- prevention, exercises for *May* 789
- Emergencies, medical symposium on, *July* 833
- Emotions, neurophysiology of *May* 744
- Empyema, pyogenic, *May* 507 510
- Encephalitis, acute emergency treatment, *July* 895
- Encephalo myelo radiculoneuritis, acute, *Jan.*, 1
- Endocarditis bacterial, subacute, penicillin in *May* 583
- brucella *March* 348
- subacute bacterial, therapeutics, *March*, 425
- Endocrine glands, real versus supposed disturbances, *July*, 1009
- system, therapeutics, *March* 433
- therapy in menstrual disorders, *Jan* 251
- Endometrial biopsy *Jan.*, 252
- Enureals ephedrine in *March* 420
- Ephedrine in asthma in children *July* 867
- in enureals, *March* 420
- in myasthenia gravis, *Jan.*, 134 *March* 421
- Epidermatophytosis, *March* 323
- Epilepsy criminal responsibility and *Jan.* 212
- electrocardiogram in, *May* 608
- glutamic acid in *March* 418
- Epinephrine in asthma in children *July* 867
- Erb's paralysis in brachial plexus injuries *Jan.*, 19
- Erysipelas, penicillin in *July*, 836
- Erysipeloid, penicillin in *July* 836
- Erythrocytes, discarded, suspension of clinical uses, *March* 432
- Erythrocytes sedimentation rate clinical significance *July* 937
- Ethylomene, *May*, 670
- Estrogen therapy in menstrual disorders, *Jan* 259
- in prostatic cancer, *March* 435
- new products, *March* 435
- Ether in oil intramuscularly in bronchial asthma *March*, 459
- Ethinyl estradiol, *March*, 435
- Exercises in pulmonary embolism prevention *May* 789
- therapeutic, in convalescence *May* 787 810
- Exhaustion states in Army and in industry *May* 771
- Expectorants in bronchial asthma, *March* 458
- Extrasystoles, quinidine in *Jan* 227
- Eye signs in brucellosis *March* 347
- FACTIAL pain, neoplasia as cause *Jan*, 91
- relief of *Jan* 73
- symptomatic, *Jan.*, 87
- Fasciculation neostigmine in *March* 422
- Fatigue "operational" *May* 729
- states in Army and in industry *May* 771
- Fats, plasma, in liver disease *July* 979
- Fear electrocardiographic changes induced by *May* 618
- Feeble-mindedness criminal responsibility and, *Jan* 208
- Feet, dermatophytosis of *March* 323
- Femoral nerve injuries, *Jan* 23
- Ferrous carbonate in facial pain *Jan* 77
- Fever therapy in brucellosis, *March*, 360
- Fibrin foam and film in neurosurgery *March*, 432
- Fibrositis, etiology, environmental factors, *May* 568
- Filariasis, postwar problem of, *July*, 903
- Fluids, administration, in diarrheas of infancy, *July* 882
- Fluorescence test for dermatophytosis *March*, 325
- Fractures in hyperparathyroidism *March*, 394
- Fret test, *May* 677
- inverted, *May*, 678
- Friedreich's disease electrocardiogram in *May* 607
- Functional tests electrocardiogram in *May* 615
- Fungus infections, pleural effusions of *March*, 508, 311
- sodium propionate in *March*, 438
- Furmetilide in bladder atony *March* 421
- Furunculosis, penicillin in *July* 836
- GALACTOSE tolerance test of liver function *July*, 977
- Gallbladder disease electrocardiogram *May* 606

- Gastric analysis, diagnostic value, *March*, 492
- Gastritis, diagnosis, *March*, 489
- gastroscopy in, *March*, 498
- Gastroduodenal disease, diagnosis, *March*, 489
- Gastrointestinal tract, acute nonsurgical emergencies related to *July*, 878
- therapeutics, *March*, 426
- Gastroscopy, *March*, 497
- Gelatin as substitute for plasma, *March*, 433
- Globin insulin in diabetes, *March*, 436
- Glomerulonephritis, acute, in children, electrocardiogram in, *May*, 606
- penicillin in, *May*, 582
- differential diagnosis, *July*, 990
- Glomerulosclerosis, intercapillary, *March*, 538
- Glucosides, cardiac, *March*, 423, 529
- Glutamic acid in epilepsy, *March*, 418
- Glycine in myasthenia gravis, *Jan*, 135
- Gonadotropin therapy in menstrual disorders, *Jan*, 256
- Gonda sign in pyramidal tract lesions, *Jan*, 57
- Gonorrhea, penicillin-resistant, *May*, 688
- Gordon's sign in pyramidal tract lesions, *Jan*, 53
- Gout, etiology, environmental factors, *May*, 567
- Grafts, nerve, *Jan*, 27
- Groin, dermatophytosis of, *March*, 323
- Guanidine in myasthenia gravis, *Jan*, 134
- Guillain-Barré syndrome, *Jan*, 1
- HEAD injuries in children, coma due to, *July*, 893
- emergency treatment, *July*, 891
- Headache, tension, *May*, 568
- Heart disease, asthma with, in children, *July*, 871
- electrocardiograms in, *May*, 595
- pain of, differential diagnosis, *March*, 513
- quinidine in, *Jan*, 215
- effect of cigarette smoking on, *July*, 949
- emergencies in pediatric practice, *July*, 871
- failure, acute, in children, *July*, 872
- congestive, with hypertension, *March*, 542
- digitals in, *March*, 524
- irregularities, electrocardiograms in, *May*, 590
- lesions in hyperparathyroidism, *March*, 395
- position, electrocardiogram and, *May*, 608
- structural abnormalities, electrocardiograms in, *May*, 595
- therapeutics, *March*, 423
- therapy in rehabilitation, *May*, 787
- Hematoma, subdural, *Jan*, 62
- chronic, diagnosis, importance of, *July*, 1042
- Hemolytic anemia, acute acquired, *May*, 695
- Hemoptysis, *July*, 837
- Hemorrhage in liver damage, control of, *March*, 432
- intracranial, convulsions of, *July*, 888
- of early pregnancy, *July*, 853
- of late pregnancy, *July*, 855
- postpartum, *July*, 855, 858
- pulmonary, idiopathic, *July*, 843
- Hemothorax, *March*, 506, 510
- Henoch's purpura, *July*, 880
- Heparin in thrombosis and embolism, *March*, 431, *July*, 933
- Herniation of intervertebral disk, *Jan*, 111
- Hexestrol, *March*, 435
- Hippuric acid test of liver function, *July*, 977
- Histamine-azoprotein in bronchial asthma, *March*, 460
- in migraine, *March*, 438
- Histoplasmosis, *March*, 337
- Hoffman sign in pyramidal tract lesions, *Jan*, 54
- Hormone assays, *Jan*, 254
- Hospitalization, intramural, need for, *May*, 812
- Hospitals, civilian, rehabilitation problem in, *May*, 808
- rehabilitation possibilities in, postwar, *May*, 725
- Hostile-aggressive reactions in returned soldiers, *May*, 735
- Hydatidiform mole, *July*, 854, 856
- Hydrochloric acid in pernicious anemia, *Jan*, 243
- Hydrothorax, *March*, 506, 510
- Hyoscine in prevention of motion sickness, *March*, 418
- Hyperinsulinism, *July*, 1014
- Hyperparathyroidism, *March*, 389
- primary, diagnosis, *July*, 1019
- Hyperpyrexia See *Fever therapy*
- Hypertension, arterial, kidneys and, clinical relationships, *March*, 535
- drug therapy, *March*, 425
- Hyperthyroidism, *July*, 1013
- thiouracil in, *March*, 302, 433
- Hypnotics in insomnia, *Jan*, 187
- Hypocalcemia, electrocardiograms in, *May*, 613
- Hypomenorrhea, hormone therapy, *Jan*, 260
- Hyperparathyroidism, treatment, *March*, 434, 435
- Hypotension, neosynephrin hydrochloride in, *March*, 420
- IMMUNE serum in brucellosis, *March*, 359
- Impetigo contagiosa, penicillin in, *July*, 836

- Industry, fatigue and exhaustion states in *May*, 771
- Inguinal buboes, *May* 668
- Injuries, head in children, coma due to *July* 893  
     emergency treatment, *July*, 891  
     peripheral nerve *Jan.*, 9
- Insanity and the criminal, *Jan* 195  
     legal conceptions *Jan*, 204  
     malingering and *Jan.*, 205
- Insomnia *Jan.*, 178  
     causes of, *Jan.*, 180  
     clinical effects, *Jan.*, 181  
     general management, *Jan* 184  
     hypnotics in, *Jan* 187  
     psychotherapy *Jan* 186  
     shock therapy in psychotic cases, *Jan* 192
- Insulin, globin, in diabetes, *March* 436  
     shock therapy in psychoses with in somnia, *Jan.*, 192
- Internal medicine in general practice symposium on *May*, 563
- Intervertebral disk, protrusion of *Jan* 111
- Intocoxrine, *March* 423
- Intracranial abscess, emergency treatment *July* 895  
     hemorrhage convulsions of *July* 888  
     Intussusception *July* 880
- Iodides in asthma in children *July* 868  
     in sporotrichosis, *March* 330
- Iodine in hyperthyroidism thioracil and *March* 310
- Iron deficiency in carcinoma of colon *July* 958
- JAUNDICE, acholuric familial type, *July* 982
- Jolly's myasthenic reaction *Jan* 129
- KEPIMINE hydrochloride *March* 420
- Kidneys, arterial hypertension and clinical relationship, *March* 535  
     infections, nontuberculous, treatment, *May*, 571  
     lesions, in hyperparathyroidism *March* 394
- Klumpke's paralysis in brachial plexus in injuries, *Jan.*, 19
- LANATOSIDE C, *March* 424
- Laryngeal diphtheria *July*, 866
- Laryngotracheobronchitis, *July* 864
- Lead poisoning in children, *July* 881  
     sodium citrate in *March* 437
- Lederer's anemia *May* 702
- Leprosy postwar problems of, *July* 907
- Lipotropic substances in cirrhosis of liver *March* 428 483 *May* 658
- Liver biopsy by aspiration *March* 365  
     cirrhosis. See *Cirrhosis of liver*  
     damage to hemorrhage in control of *March* 432
- Liver diseases, diet as factor *March*, 276 427, 484  
     dysfunction constitutional, *July* 982  
     functional tests, *July*, 973  
         composite *March* 363  
     therapy in pernicious anemia, *Jan* 242
- Lobectomy in tuberculosis *March* 451
- Lumbago etiology, *May* 568
- Lung abscess, emergency aspects, *July* 841  
     carcinoma emergency aspects, *July* 842  
     cystic disease, emergency aspects, *July* 845  
     edema of acute, emergency aspects, *July*, 837  
     resection in tuberculosis, *March* 451
- Lymphocytic choriomeningitis benign *Jan.*, 36
- Lymphogranuloma venereum *May* 663  
     diagnosis, *May* 677  
     extragenital, *May* 675  
     treatment, *May* 682
- Lymphorrhoids in lymphogranuloma venereum, *May*, 670 671
- MAGNESIUM sulfate in paroxysmal tachycardia *March*, 426
- Maladjustment, transitory in soldiers, reconditioning in *May* 751
- Malaria postwar problem of *July* 902  
     reconditioning the patient *May* 760
- Malingering of insanity to escape criminal responsibility *Jan* 205
- Malta fever See *Brucellosis*
- Mandelic acid in urinary tract infections, *May* 574 576
- Massage in rehabilitation, *May* 787
- Mecholyl effects on electrocardiogram *May* 614  
     in bronchial asthma *March*, 459
- Median nerve injuries, *Jan.*, 11
- Median ulnar nerve injuries, *Jan.*, 18
- Medical emergencies, symposium on *July* 833
- Medullary tractotomy for facial pain, *Jan*, 84
- Melms syndrome, pleural effusion in *March* 509, 512
- Meningitis, acute emergency treatment, *July* 895  
     coma of emergency treatment, *July* 893  
     lymphocytic, benign *Jan*, 36  
     pneumococcal penicillin in *May* 585
- Menopause *July* 1015  
     male *July*, 1015
- Menorrhagia hormone therapy *Jan.*, 259 261, 264, 266
- Menstruation disorders of diagnostic aids, *Jan.*, 252  
     endocrine therapy *Jan.*, 251
- Mental disease criminal responsibility and *Jan*. 195

- Mental retardation, criminal responsibility and, *Jan*, 208  
 Mercupurin as diuretic, *March*, 424  
 Methenamine in urinary tract infections, *May*, 574, 575  
 Methionine in cirrhosis of liver, *March*, 429, 484  
 Microsporion infections, *March*, 323  
 Migraine, histamine-azoprotein in, *March*, 438  
 Miscarriage See *Abortion*  
 Mole, hydatidiform, *July*, 854, 856  
 Monilia albicans, infections with, *March*, 323, 328  
 Monoacetylmorphine, *March*, 418  
 Monocaine for local anesthesia, *March*, 419  
 Motion sickness, treatment, *March*, 418  
 Mouth wash in pernicious anemia, *Jan*, 245  
 Musculocutaneous nerve injuries, *Jan*, 23  
 Myasthenia gravis, diagnostic tests, *Jan*, 128, *March*, 422  
     management, *Jan*, 126, 129  
     treatment, advances in, *March*, 421  
 Myasthenic reaction of Jolly, *Jan*, 129  
 Mycology, medical, *March*, 323  
 Myocardial infarction, restriction of activity in coronary occlusion in relation to, *March*, 405  
 Myocarditis, Fiedler's, electrocardiogram in, *May*, 606  
 Myxedema, *July*, 1012
- NARCOLEPSY in children, *July*, 894  
 Narcosynthesis in war neurosis, *May*, 737  
 Neck, painful, *May*, 568  
 Needle liver biopsy, *March*, 365  
 Neoarsphenamine in urinary tract infections, *May*, 577  
 Neostigmine in fasciculation, *March*, 422  
     in myasthenia gravis, diagnostic, *March*, 422  
     therapeutic, *March*, 421  
     in poliomyelitis, *March*, 423  
     in rheumatoid arthritis, *March*, 423  
 Neosynephin hydrochloride, uses, *March*, 420  
 Nephritis, differential diagnosis, *July*, 990  
     in children, *July*, 874  
 Nephrocalcinosis in hyperparathyroidism, *March*, 394  
 Nephrosis in children, *July*, 874  
     testosterone in, *March*, 436  
 Nerve grafts, *Jan*, 27  
 Nerves, peripheral, injuries, diagnosis and surgical treatment, *Jan*, 9  
 Nervous disease, organic origin in apparent functional cases, *Jan*, 30  
     system, autonomic, therapeutics, *March*, 419  
     central, therapeutics, *March*, 417  
 Neuralgia, trigeminal, *Jan*, 73
- Neuralgia, trigeminal, atypical, *Jan*, 85  
     symptomatic, *Jan*, 75  
 Neurocirculatory asthenia, electrocardiogram in, *May*, 617  
 Neurologic emergencies, nonsurgical, in children, *July*, 886  
 Neuromuscular apparatus, therapeutics, *March*, 421  
 Neuropsychiatric diseases, symposium on, *Jan*, 1  
 Neuroses in combat crews overseas, *May*, 731  
     in returned soldiers, *May*, 733  
     war, *May*, 729  
 Neurosurgery, fibrin film and foam in, *March*, 433  
 Neurotomy, retrogasserian, classical, for facial pain, *Jan*, 80  
     posterior, for facial pain, *Jan*, 83  
 New developments in medicine, symposium on, *March*, 273  
 Nicotine, effects on electrocardiogram, *May*, 612  
     intravenous administration, effect on heart and peripheral blood vessels, *July*, 949  
 Nicotinic acid, effects on electrocardiogram, *May*, 614  
 Nocardia asteroides, infection with, *March*, 340  
 Nutrition in rehabilitation, *May*, 794  
 Nutritional deficiency diseases See *Deficiency diseases*
- OBSTETRICS, nonsurgical emergencies in, *July*, 848  
 Occupational therapy in rehabilitation, *May*, 788  
 Octofollin, *March*, 435  
 Oliguria in infants and children, *July*, 874  
 Omentopexy in cirrhosis of liver, *March*, 281  
 Oneirophrenia, *Jan*, 162  
 Operational fatigue, *May*, 729  
 Oppenheim's sign in pyramidal tract lesions, *Jan*, 52  
 Opsonocytophagic test for brucellosis, *March*, 354  
 Organic origin of apparent functional nervous disease, *Jan*, 30  
 Osteitis fibrosa cystica generalisata, *March*, 389, 395  
 Osteoarthritis, etiology, environmental factors, *May*, 567  
 Ouabain, *March*, 424
- PAIN, facial, neoplasia as cause, *Jan*, 91  
     relief of, *Jan*, 73  
     symptomatic, *Jan*, 87  
     intractable, chordotomy for, *Jan*, 98  
     precordial, differential diagnosis, *March*, 513  
 Pancreas, disturbances, *July*, 1014

- Pancreatic insufficiency pancreas and  
 zyme in, *March*, 42  
 Pancreatitis, acute, *March*, 42  
 May 60  
 Paracetamol in carbons of liver *March*  
 281  
 Paralysis, cerebral, *March*, 42  
 792 819  
 Erb's, *Jan.*, 19  
 familial periodic, *March*, 42  
 422  
 Klumpke's, *Jan.*, 19  
 Paraphimosis in children, *July* 8  
 Parasympathetic drugs, *March* 4 1  
 Parathyroid insufficiency, *July* 1013  
 Parathyroids, diseases of, *March* 3, 9  
 Paredrine, uses, *March* 420  
 Paredrinol, uses, *March* 420  
 Parotitis, epidemic, electrocardiogram in,  
*May* 607  
 Passive dependent reactions in returned  
 soldiers, *May* 744  
 Patek's diet in carbons of liver *March*  
 276  
 Patellar clonus in pyramidal tract lesions  
*Jan.*, 57  
 Pellagra, diet in, *May* 803  
 Penicillin in anthrax, *July* 835  
 in burns infection, *July* 836  
 in carbuncles, *July* 836  
 in cavernous sinus thrombosis, *July*  
 894  
 in cellulitis, *May* 584 *July* 836  
 in erysipelas and erysipeloid, *July* 836  
 in furunculosis, *July* 836  
 in glomerulonephritis, *May* 582  
 in impetigo contagiosa, *July* 836  
 in lymphogranuloma venereum, *May*  
 652  
 in pneumococcal meningitis, *May* 585  
 in pneumonia, *May* 580 582  
 in subacute bacterial endocarditis, *May*  
 583  
 in urinary tract infections, *May* 574  
 578  
 Inhalant, *July*, 916  
 methods of administration and dosage  
*July* 909  
 snuff *July*, 916  
 versus sulfonamide therapy *May* 5, 9  
 Pentothal narcosynthesis in war neuroses  
*May* 737  
 Peptic ulcer benign and malignant, dif-  
 ferentiation, *March*, 495  
 chronic appendicitis simulating *May*  
 629  
 diagnosis, *March* 489  
 diet in, fundamental importance in  
 Army hospital *May* 706  
 differential diagnosis, *May* 624  
 gastric catarrh with *May* 628  
 gastroscopy in *March* 499  
 in asthenic person *May* 625  
 in hypersthenic person *May* 626

- Pneumonia, emergency aspects, *July*, 840  
in children, *July*, 868  
penicillin in, *May*, 580, 582  
pneumococcal, sulfamerazine in, *March*, 294  
postoperative, prevention, breathing exercises for, *May*, 789  
Pneumothorax, spontaneous, emergency aspects, *July*, 844  
Poisons, ingestion, by children, management, *July*, 884  
Polomyelitis, neostigmine in, *March*, 423  
physical medicine in, *May*, 791  
Polyuria in hyperparathyroidism, *March*, 395  
Postpartum hemorrhage, *July*, 855, 858  
infections, *July*, 859  
Potassium chloride in cataplexy, *March*, 422  
in myasthenia gravis, *Jan*, 135  
salts, effects on electrocardiogram, *May*, 613  
Pouredign, *March*, 423  
Precordial pain, differential diagnosis, *March*, 513  
Pre-eclampsia, *March*, 538, 541, *July*, 850  
Pregnancy, early, hemorrhage of, *July*, 853  
ectopic, ruptured, *July*, 854, 856  
late, hemorrhage of, *July*, 855  
macrocytic anemia of, *Jan*, 247  
pernicious vomiting of, *July*, 848  
toxemia of, *July*, 848  
Prepuce, redundant, *July*, 877  
Procaine hydrochloride for local anesthesia, *March*, 419  
Proctitis in lymphogranuloma venereum, *May*, 673  
Progesterone therapy in menstrual disorders, *Jan*, 263  
Promin in tuberculosis, *March*, 447, 448, *July*, 919  
Promizole in tuberculosis, *July*, 921  
Propadrine in asthma in children, *July*, 867  
in coryza, *March*, 420  
Propionate-propionic acid ointment in dermatophytosis, *March*, 326  
Prostate, carcinoma, estrogen therapy, *March*, 435  
Prostigmine in myasthenia gravis, *Jan*, 131  
diagnostic test, *Jan*, 128  
Protein, serum, in liver disease, *July*, 979  
Prothrombin time in dicoumarol therapy, *July*, 930  
in liver disease, *July*, 978  
Protrusion of intervertebral disk, *Jan*, 111  
Psychiatric disorders in combat crews  
overseas, *May*, 729  
returnees, *May*, 733  
Psychiatrist, function of, in court, *Jan*, 211  
Psychological readjustment in rehabilitation program, Army Air Forces, *May*, 723  
Psychoneurosis, transitory, in soldiers, reconditioning in, *May*, 751  
Psychoses, criminal responsibility in, *Jan*, 195  
electroshock therapy, outpatient, *Jan*, 165  
war, barbiturates in, *March*, 418  
with insomnia, electroshock and insulin shock therapy, *Jan*, 192  
Psychosomatic aspects of rehabilitation, *May*, 740  
principles, *May*, 742  
states, in combat crews, *May*, 732  
in returned soldiers, *May*, 736  
Psychotherapy in fatigue and exhaustion states, *May*, 781  
in insomnia, *Jan*, 186  
in war neuroses, *May*, 737  
Psychotic-like states in combat crews, *May*, 732  
in returned soldiers, *May*, 736  
Puerperal sepsis, *July*, 859  
Pulmonary embolism, electrocardiograms in, *May*, 605  
emergency aspects, *July*, 839  
prevention, exercises for, *May*, 789  
Pulsus alternans, electrocardiogram in, *May*, 617  
Purpura, Henoch's, *July*, 880  
Pyelonephritis, acute diffuse, in children, *July*, 875  
atrophic, *March*, 541  
in hyperparathyroidism, *March*, 394  
Pyramidal tract signs, pathologic, *Jan*, 45  
QUICK prothrombin time test in dicoumarol therapy, *July*, 930  
Quinidine, effects on electrocardiogram, *May*, 611  
in auricular fibrillation, *Jan*, 217  
in auricular flutter, *Jan*, 223  
in paroxysmal tachycardia, *Jan*, 226  
uses and abuses, *Jan*, 215  
Quinine test for myasthenia gravis, *Jan*, 129, *March*, 422  
RACEPHEDRINE hydrochloride, *March*, 420  
Radial nerve injuries, *Jan*, 10  
Radiculoneuritis, acute infectious, *Jan*, 1  
Raynaud's disease, diagnosis, *July*, 942  
Reconditioning of malaria patient, *May*, 760  
of transitorily maladjusted soldiers, *May*, 751  
program, Army, *May*, 788  
Army Air Forces, *May*, 717  
Rectum, stricture, in lymphogranuloma venereum, *May*, 673, 674, 683

- Rehabilitation, Federal State and in  
   dus try's interest in *May* 817  
   in Army Air Forces, *May* 715  
   in civilian medical practice, *May*, 807  
   nutrition in *May* 794  
   of malaria patient *May* 760  
   of rheumatic fever patients, *May* 765  
   of transitorily maladjusted soldiers,  
     *May* 751  
   physical medicine in, *May* 786  
   postwar possibilities, *May* 725  
   psychosomatic aspects, *May*, 740  
   symposium on, *May* 714  
 Respiratory tract, nonsurgical emergen-  
   cies in childhood *July* 864  
 Retrogasserian neurotomy classical for  
   facial pain, *Jan* 80  
   posterior for facial pain *Jan*, 83  
 Returnees, psychiatric disorders in, *May*  
   733  
 Rheumatic conditions, etiology environ-  
   mental factors *May* 566  
 Rheumatic fever convalescence physical  
   fitness testing and physical train-  
   ing in *May* 719  
   in Army Air Forces convalescent  
   care *May* 765  
   penicillin failure in *May* 580  
   pleural effusion in *March* 508  
   present-day concepts *July* 923  
   sodium salicylate in *March*, 425  
   sulfadiazine in, prophylactic, *March*  
     425  
 Rheumatoid arthritis etiology environ-  
   mental factors *May* 566  
   neostigmine in, *March* 423  
 Riboflavin deficiency diet in, *May* 805  
 Ringworm, *March* 323  
 Roentgen appearance of skeletal changes  
   in hyperparathyroidism *July* 1028  
   diagnosis of carcinoma of stomach  
     *March* 495  
   of peptic ulcer *March* 493  
   of tuberculosis rapid screening  
     methods, *March* 544  
 Roentgenoscopy protection in *July*  
   1036  
 Rossolino sign in pyramidal tract le-  
   sions, *Jan*., 53  
 SALYRGAN THEOPHYLLINE as diuretic,  
   *March* 424  
 Sandfly fever postwar problem of *July*  
   901  
 Sandoz, *March* 424  
 Scalp dermatophytosis of *March* 323  
 Schistosomiasis postwar problem of  
   *July* 907  
 Schizophrenia, *Jan*., 150  
   modern concept of, *Jan*., 147  
   Sciatic nerve injuries, *Jan*., 40  
   Sciatica *May* 569  
 Sclerosis, posterolateral, management in  
   pernicious anemia *Jan*., 245  
 Scurvy diet in *May* 803  
 Sedatives in psychosomatic disorders,  
   abuse of, *May* 748  
 Sedimentation rate of erythrocytes clin-  
   ical significance *July* 937  
 Sepsis, puerperal, *July* 859  
 Sex glands, disturbances *July* 1015  
 Shock in burns, sodium lactate in  
   *March* 438  
   therapy of psychoses, *Jan*., 165  
   prevention of fractures curare for  
     *March* 423  
 Shoulder painful *May* 569  
 Sign of the groove in lymphogranuloma  
   venereum *May* 668 669  
 Silicosis aluminum powder in *March*  
   437  
 Sinus thrombosis, cavernous, emergency  
   treatment *July* 894  
 Skin test in brucellosis, *March* 354  
 Sleeplessness, *Jan*., 178  
   clinical effects *Jan*., 181  
   treatment *Jan* 184  
 Sodium alkyl sulfate in peptic ulcer,  
   *March* 426  
   citrate in lead poisoning *March* 437  
   lactate in burn shock *March* 438  
   propionate in fungus infections, *March*  
     438  
   salicylate in rheumatic fever *March*  
     425  
   sulfanilyl sulfanilate in lymphogranu-  
     loma venereum *May* 682  
 Soldiers, combat psychiatric disorders  
   in *May* 729  
   returned from combat psychiatric dis-  
   orders in *May* 733  
   transitorily maladjusted recondition-  
   ing of *May* 751  
   veteran psychosomatic disorders in  
     *May* 740  
 Spiller Frazier operation for facial pain  
   *Jan*., 80  
 Splenectomy in hemolytic anemia *May*  
   704  
 Spontylitis, brucella, *March* 351  
 Sporotrichosis, *March* 328  
 Steam inhalations in bronchial asthma  
   *March* 458  
 Steatorrhea, pancreatic, pancreatic en-  
   zyme in *March* 429  
 Sterility hormone therapy *Jan*., 258 261  
 Stomach carcinoma, diagnosis, *March*  
   489  
 Streptomycin in tuberculosis *July* 922  
 Streptotrichosis *March* 340  
 Strobanthin in heart failure *March*,  
   529  
 Strychnine poisoning, convulsions of  
   *July* 889  
 Subdural hematomas *Jan*., 62  
   chronic, diagnosis, importance of  
     *July* 1042  
 Succinylsulfathiazole See *Sulfam*



- Sulfadiazine in lymphogranuloma venereum, *May*, 682  
 in rheumatic fever, prophylactic, *March*, 425  
 in urinary tract infections, *May*, 576  
 Sulfamerazine in pneumococcal pneumonia, *March*, 294  
 Sulfasuxidine in bacillary dysentery, *March*, 426  
 Sulfathalidine in bacillary dysentery, *March*, 426  
 in chronic ulcerative colitis, *March*, 427  
 Sulfathiazole in lymphogranuloma venereum, *May*, 682  
 in urinary tract infections, *May*, 576  
 Sulfonamides in brucellosis, *March*, 357  
 in cavernous sinus thrombosis, *July*, 894  
 in diarrheas of infancy, *July*, 884  
 in lymphogranuloma venereum, *May*, 682  
 in tuberculosis, *March*, 447  
 in urinary tract infections, *May*, 574, 576  
 insoluble, in intestinal diseases, *March*, 426  
 urinary disturbances due to, in children, *July*, 877  
 versus penicillin, *May*, 579  
 Sulkowitch test in hyperparathyroidism, *July*, 1026  
 Suprapatellar reflex in pyramidal tract lesions, *Jan*, 57  
 Suture, primary, in peripheral nerve injuries, *Jan*, 25  
 Sympathomimetic drugs, new, *March*, 419  
 Syphilis, cardiovascular, electrocardiogram in, *May*, 606  
 dichlorophenarsine hydrochloride in, *March*, 438  
 TACHYCARDIA, paroxysmal, digitalis in, *March*, 531  
 in children, *July*, 873  
 magnesium sulfate in, *March*, 426  
 quinidine in, *Jan*, 226  
 Talma operation in cirrhosis of liver, *March*, 281  
 Testosterone in menstrual disorders, *Jan*, 265  
 in nephrosis, *March*, 436  
 Tests, functional of liver, *July*, 973  
 Tetanus, convulsions of, *July*, 889  
 curare in, *March*, 423  
 Tetany in infants and children, convulsions of, *July*, 890  
 parathroid, prevention, *March*, 402, 434  
 Thiamine hydrochloride in facial pain, *Jan*, 77  
 Thiouracil, clinical development and application, *March*, 303, 306  
 in thyrotoxicosis, *March*, 302, 433  
 toxicity, *March*, 307  
 Thoracentesis, *March*, 503  
 Thoracic disease, nonsurgical emergencies, *July*, 837  
 Thoracoplasty in tuberculosis, *March*, 449  
 Thrombo-angitis obliterans, physical medicine in, *May*, 791  
 Thrombosis, cerebral, in children, *July*, 894  
 coronary, *March*, 405  
 pain of, differential diagnosis, *March*, 513  
 prevention, dicoumarol in, *July*, 929  
 heparin in, *July*, 933  
 venous, heparin in, *March*, 431  
 Thrush, *March*, 323, 328  
 Thymectomy for myasthenia gravis, *Jan*, 136  
 Thymus, emergencies associated with, *July*, 860  
 Thyroid extract, effects on electrocardiogram, *May*, 611  
 in familial periodic paralysis, *March*, 422  
 gland, disturbances, real versus supposed, *July*, 1012  
 Thyrotoxicosis, thiouracil in, *March*, 302, 433  
 Tibial nerve injuries, *Jan*, 22  
 Tinea, *March*, 323  
 Torulosis, *March*, 335  
 Toxemia of pregnancy, *July*, 848  
 preeclamptic, *July*, 850  
 Tractotomy, medullary, for facial pain, *Jan*, 84  
 Transfusions, blood, in hemolytic anemia, *May*, 703  
 in pernicious anemia, *Jan*, 245  
 Trends, modern, in internal medicine, *May*, 563  
 Trichinosis, electrocardiogram in, *May*, 607  
 Trichlorethylene in facial pain, *Jan*, 77  
 Trichophytin test for dermatophytosis, *March*, 325  
 Trichophytosis, *March*, 323  
 Trigeminal neuralgia, *Jan*, 73  
 atypical, *Jan*, 85  
 symptomatic, *Jan*, 75  
 Trigger zones in trigeminal neuralgia, *Jan*, 74  
 Trömner's technic for Hoffmann sign, *Jan*, 54  
 Tropical diseases, postwar aspects, *July*, 897  
 Trypanosomiasis, postwar problem of, *July*, 906  
 Tuamne sulfate, *March*, 420  
 Tuberculosis, chemotherapy, *March*, 445, *July*, 918  
 diasone in, *March*, 447, 448, *July*, 921  
 physical medicine in, *May*, 792  
 promin in, *March*, 447, 448, *July*, 919  
 promizole in, *July*, 921





John W. Strieder, M.D. Assistant Professor of Thoracic Surgery, Boston University School of Medicine, Boston, Massachusetts, Visiting Surgeon in Charge of Thoracic Surgery, Massachusetts Memorial and Boston City Hospitals

Walter B. Talbot, M.D. Assistant Professor of Pediatrics, Harvard Medical School, Assistant Physician Massachusetts Memorial Hospital

Samuel N. Vose, M.D., F.A.C.S. Professor of Genitourinary Surgery, Boston University School of Medicine, Surgeon-in-Chief, Genitourinary Department, Massachusetts Memorial Hospitals, Boston.

Robert W. Wilkins, M.D., Associate Professor of Medicine, Boston University School of Medicine, Physician, Massachusetts Memorial Hospitals, Member Evans Memorial, Massachusetts Memorial Hospitals

---

## CONTENTS

### SYMPOSIUM ON SPECIFIC METHODS OF TREATMENT

	PAGE
Indications and Uses of Blood, Blood Derivatives and Blood Substitutes	1069
By Drs. Charles A. Janeway, William Berenberg and Gretchen Hutchins	
Treatment of Common Dermatoses	1095
By Dr. John G. Downing	
The Treatment of Epilepsy	1114
By Dr. William G. Lennox	
The Treatment of Nonhemolytic Streptococcus Subacute Bacterial Endocarditis with Penicillin	1129
By Drs. Donald G. Anderson and Chester S. Keefer	
The Management of Cardiac Emergencies	1154
By Captain James M. Faulkner	
The Therapeutic Control of Recurrent Peptic Ulcer	1162
By Drs. Franz J. Ingelfinger and Robert E. Moss	
Specific Therapy in Acute Hemorrhagic Nephritis	1173
By Drs. Allan M. Butler and Gertrud C. Reversbach	
Management of the Patient with Chronic Diffuse Glomerulonephritis	1184
By Dr. Stanley E. Bradley	

# CONTENTS

	PAGE
The Management of Some Common Disturbances of the Female Bladder Function By Dr Samuel N Vose	1200
Management of the Medical Convalescent By Dr Robert W Wilkins	1210
Obesity in Children By Dr Nathan B Talbot	1216
Practical Psychiatry By Dr Harry C Solomon	1231
Active Immunization against Some Common Communicable Diseases By Drs Matthew A Derow and Sanford B Hooker	1238
Conductive Deafness and Its Relation to Lymphoid Hyperplasia of the Nasopharynx. Benefits from X-ray Therapy By Drs Edward B D Neuhauser and Charles F Ferguson	1251
The Treatment of Meningitis By Dr John A. V Davies	1259
— The Treatment of Common Arthritic Conditions By Dr Francis Cooley Hall	1269
Surgical Indications and Treatment of Primary Cancer of Lung, Bronchiectasis and Lung Abscess By Dr John W Strieder	1282
— Vitamins in Present Day Treatment By Dr Harold Jeghers	1294
The Present Status of Sulfonamide Therapy By Dr Francis C Lowell	1306
— Laboratory Findings in the Blood and Urine in Health and Disease By Dr Stanley E Bradley	1314
Cumulative Index	1327

# THE MEDICAL CLINICS of NORTH AMERICA

Vol-29

1945

BOSTON NUMBER

## SYMPOSIUM ON SPECIFIC METHODS OF TREATMENT

### INDICATIONS AND USES OF BLOOD BLOOD DERIVATIVES AND BLOOD SUBSTITUTES

CHARLES A. JANEWAY M.D \* WILLIAM BERENBERG, M.D † AND  
GRETCHEN HUTCHINS, M.D ‡

#### I PHYSIOLOGICAL BACKGROUND FOR THE USE OF BLOOD AND ITS DERIVATIVES

**Introduction**—The discovery of the blood groups by Landsteiner made the transfusion of human blood from one individual to another a safe procedure, while the development of methods for indirect transfusion by the use of sodium citrate as an anticoagulant, and the ingenious device of the "blood bank" have made it a practicable one. In recent years there have been developed a series of blood derivatives—plasma, serum resuspended red cells, and the products of plasma fractionation—which have replaced whole blood in many instances and have had new and important applications to the treatment of disease. In addition to these blood *derivatives*, a number of blood *substitutes* have been proposed and tested the earliest of these being gum acacia, which was first used in 1917. It is the purpose of this clinic to outline, as succinctly as possible, the best practice at present in this rapidly expanding field of therapy.

*The rational use of blood and its derivatives presupposes a basic understanding of its physiology.* Blood is a complex mixture of components with many different functions and properties and derived

From the Department of Pediatrics, Harvard Medical School and School of Public Health and from the Children's and Infants' Hospitals, Boston.

\* Assistant Professor of Pediatrics, Harvard Medical School Visiting Physician, Children's and Infants' and Peter Bent Brigham Hospitals.

† Instructor in Pediatrics, Harvard Medical School Junior Attending Physician, Children's and Infants' Hospitals.

‡ Assistant in Pediatrics, Harvard Medical School Junior Attending Physician, Children's and Infants' Hospitals.

from many parts of the body. Because of its multiple constituents, blood has naturally been used for many therapeutic indications. The present trend is toward the use of the specific component needed by the patient whenever it is available, rather than the administration of whole blood for all purposes, as was common practice until a few years ago. This is both more economical and more efficacious. In correcting deficiencies of particular components, two general types of therapy may be used—replacement or stimulation. *Replacement* consists in the passive transfer of the missing component from an outside source and is frequently a matter of urgent necessity. *Stimulation* consists in providing the stimulus to the manufacture of the missing component by the patient, with gradual but more lasting results if the patient is able to respond.

**Functional Components of Blood**—Blood is a suspension of cellular elements in a fluid matrix, the plasma.

TABLE 1 —CELLULAR ELEMENTS OF THE BLOOD

Physiologic Data			Therapeutic Data		
Component	Source	Function	Replacement	Stimulation	Disease
Red blood cells	Bone marrow	Oxygen transport	Whole blood Resuspended cells	Liver extract Iron Vitamins B+C Thyroid	Hemorrhage Hemolytic anemia Aplastic, myelophthitic and azotemic anemia Pernicious anemia Hypochromic anemia Deficiency Hypothyroidism
Polymorphonuclear leukocytes	Bone marrow	Phagocytosis, defense against infection	(Whole blood)	(Crude liver extract) Stop offending drug or control infection	Agranulocytosis
Eosinophilic and basophilic leukocytes	Bone marrow	?			
Lymphocytes	Lymph nodes	?			
Monocytes	Tissues	Phagocytosis			
Platelets	Megakaryocytes of bone marrow	Clot retraction	Fresh whole blood (Fresh Plasma)	Stop offending drug or control infection	Thrombocytopenic purpura

Parentheses denote treatment of doubtful value

**Cellular Elements**—From the clinical standpoint, three groups of cellular elements are important—the red blood cells, which normally constitute approximately 40 per cent of the total blood volume, the white blood cells, and the platelets. A brief summary of our knowledge of these components is given in Table I.

**Plasma Proteins**—Sixty per cent of the total blood volume of a normal individual consists in plasma, an aqueous solution containing many solutes but principally sodium, chloride and bicarbonate ions, glucose, simple nitrogenous com-

TABLE 2 --PRINCIPAL PLASMA PROTEINS OF THERAPEUTIC IMPORTANCE

Physiologic Data				Therapeutic Data		
Component	Type of Protein	Source	Function	Replacement	Stimulation	Disease
Albumin	Albumin	Liver	Maintenance of blood volume available for nutrition	Human serum albumin (Plasma or serum 1 2 3+)	Amino acids High protein high caloric diet	Shock Hypoproteidemia
Prothrombin	Beta globulin	Liver	Precursor of thrombin (clotting enzyme)	Plasma 2 Fresh blood	Vitamin K	Jaundice (obstructive) Liver damage Dicoumarin poisoning
Fibrinogen	Globulin	Liver	Precursor of fibrin (material of clot)	Plasma 2, 3 Fresh blood		Severe liver damage
Hemophilic globulin	Globulin	?	Acceleration of clotting	Plasma 2 (3)		Hemophilia
Antibodies	Gamma globulin	Reticuloendothelial system	Humoral immunity	Immune serum globulin Pooled (normal) or convalescent plasma or serum	Active immunization	Infectious diseases, malaria, infectious hepatitis, the scarlet fever
Complement	Alpha and beta globulins	?	Accelerates immune reaction in vitro (hemolysis, bacteriolysis)	Plasma 2 (3) Fresh blood	?	?
Isohemagglutinins	? gamma globulin	?	?	Use in blood grouping for transfusion		

+ Plasma or serum. 1 = Liquid; 2 = Frozen 3 = Dried  
 Parentheses = Less desirable therapy



pounds, and proteins. It is the concentration of the latter (7 per cent) which chiefly distinguishes plasma from its filtrate, the interstitial fluid.

The plasma proteins are a large and diverse group of molecular species ranging from the relatively symmetrical albumin molecule, with its small size and high net charge giving it its osmotic potency, to the long rod-shaped fibrinogen molecule, specially suited to the formation of the tangled fibrillar structure of the clot. In recent years separation of these proteins into fractions in which specific functions are concentrated has been achieved<sup>1</sup> and these products of plasma fractionation, developed from blood collected by the American Red Cross for the armed forces, will undoubtedly find their way into civilian medicine in due time. The principal plasma proteins of importance to the physician have been recorded in Table 2.

*Water and Electrolytes*—Neither the blood cells nor the plasma proteins would be of much use without water, which is the principal constituent of the body, comprising approximately 70 per cent of its weight. Body water is distributed between three "compartments"—(1) the cells, (2) the interstitial fluid and (3) the plasma—in accordance with complex osmotic equilibria which depend

TABLE 3 —BODY WATER

	Total Volume	Per Cent of Total Body Weight	Principal Cations	Principal Anions	Protein Conc.
Intracellular fluid	35 liters	50	K <sup>+</sup> , Ca <sup>++</sup> , Mg <sup>++</sup>	HPO <sub>4</sub> <sup>-</sup>	20-30%
Cell Walls					
Interstitial fluid (includes spinal fluid, aqueous humor)	10.5 liters	15	Na <sup>+</sup>	Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup>	0.1-1 % (Lymph may run as high as 3-4%)
Capillary Walls					
Plasma	3.5 liters	5	Na <sup>+</sup>	Cl <sup>-</sup> , HCO <sub>3</sub> <sup>-</sup>	7%

Plasma and interstitial fluid = extracellular fluid

upon the respective permeabilities of the different membranes separating the "compartments" (see Table 3).<sup>2</sup> From the practical standpoint, the volume of extracellular fluid is maintained by the kidney which regulates it by its control of the excretion of water and sodium ions, while the volume of plasma is maintained by the plasma proteins, principally albumin, since the capillary walls are largely impermeable to protein molecules although freely permeable to sodium and other ions and small molecules. In any consideration of replacement therapy, it is essential not to forget the importance of the three cardinal solutions for parenteral use—physiological saline for the replacement of extracellular fluid, glucose for the provision of water and calories, and sodium bicarbonate or lactate for the correction of acidosis. Restoration of kidney function is an essential feature of the treatment of shock, and this involves both the restoration of blood volume to provide an adequate renal circulation and the provision of sufficient fluid for excretion.

*Laboratory-Control of Replacement Therapy*—The accurate, recognition and proper treatment of disturbances of the various functional

components of blood and body fluids require constant control. One of the chief difficulties in the use of these methods only measure concentrations of substances in the blood, the total amounts present. Thus they are of limited value in the

TABLE 4—OBSERVATIONS OF VALUE IN THE FOLLOWING CONDITIONS: HEMORRHAGE, TRAUMATIC SHOCK, BURN, AND THE FOLLOWING FLUID AND ELECTROLYTE DEFICIENCIES

Observations	Method	
--------------	--------	--

A. Laboratory

Hemoglobin or hematocrit	Hemoglobin Hematocrit reading Whole blood specific gravity	
Total protein	Serum or plasma specific gravity	
Chloride	Serum chloride	
CO <sub>2</sub>	CO <sub>2</sub> combining power of serum or blood	
Nonprotein nitrogen	N.P.N. or BUN of serum or blood	
Urine volume	12 or 24 hour collection	
Urine specific gravity	Specific gravity	

Skin temperature of extremities	Fat content of skin
Hydration of skin	Impulse of skin
Pulse	Pulse rate
Blood pressure	Blood pressure
Peripheral edema	Edema
Pulmonary edema	Pulmonary edema

three-dimensional  
anemic picture  
normal if  
result of

transfusion is  
uses the num-  
ing capacity of  
mia due either to  
transfusion is often  
forms of anemia,  
of of symptoms,  
care and general  
tial measures are

has been

of blood volume is devised, we shall continue to labor under this handicap

However, it is possible to obtain much valuable information on changes taking place in patients by the combination of a few relatively simple laboratory measurements and clinical observations, which should be routine procedures in any hospital caring for acutely ill patients, particularly surgical patients (see Table 4 and Fig 161)

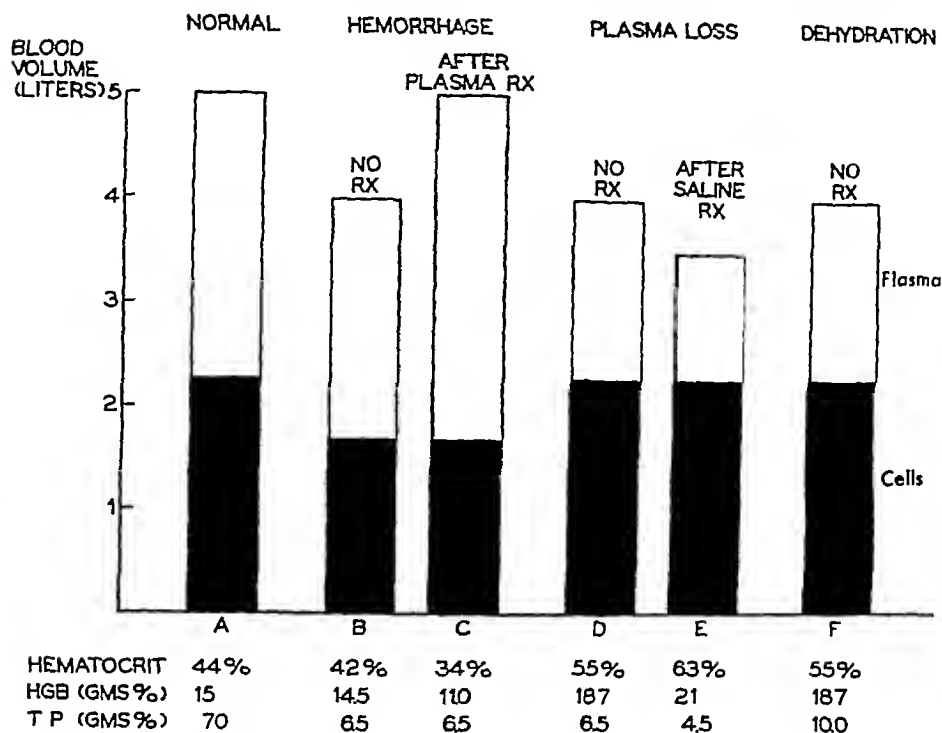


Fig 161—Schematic diagram of changes in blood volume and principal blood values after loss of body fluids *A*, Normal, *B*, immediately after hemorrhage (note slight hemodilution), *C*, same after adequate replacement with plasma (note anemia), *D*, after plasma loss from burn (note hemoconcentration with normal plasma proteins), *E*, same after saline (note further fall in plasma volume and hypoproteinemia), *F*, dehydration (note hemoconcentration with high serum proteins)

Perhaps the most useful addition to the methods for following the progress of therapy in patients with shock or burns has been the introduction of simple methods for the determination of specific gravity of biological fluids. The so-called "falling drop" method has been used clinically for a number of years,<sup>8</sup> but recently a new method, making use of copper sulfate solutions, has been introduced.<sup>4</sup> By this method the specific gravity of whole blood, which is a relatively accurate measure of the hemoglobin concentration, and the specific gravity of the plasma, which is a good measure of the plasma protein concentration, can be determined with a very small sample of blood by any technician in a few minutes, the only equipment necessary being a few bottles of standardized copper sulfate solution and a centrifuge. These two values give the important data for

the proper control of replacement therapy in case of burns, hemorrhage, or traumatic shock. In cases of shock, values obtained with capillary blood are less accurate than with venous blood, which should be drawn without stasis if possible. All specific gravity methods of plasma protein determination although sufficiently accurate for clinical use in most situations, give very erroneous results in instances of the nephrotic syndrome, where the high lipid content of the plasma lowers the specific gravity.

## II THE USE OF WHOLE BLOOD

**Indications.**—**LOSS OF WHOLE BLOOD**—*Hemorrhage*—In hemorrhage one loses all the constituents of whole blood and only whole blood can adequately replace it. When hemorrhage is attended by shock, plasma may be used to increase blood volume while whole blood is being obtained. Fresh blood has no real advantage over properly handled bank blood in the replacement treatment of hemorrhage.

*Burns*—Although the administration of plasma is the treatment of choice for combating shock due to burns, the transfusion of whole blood is indicated when plasma is not readily available. Even if hemocoagulation is present in the patient, such a transfusion is reasonable for the donor's blood is relatively dilute by comparison.<sup>5</sup> Whole blood is indicated when the burned patient has suffered significant hemorrhage. Some of these patients develop hemolytic phenomena,<sup>6</sup> and after the first few days most of them develop secondary anemia of the deficiency type, so that transfusion of whole blood may be indicated in therapy for any of these conditions.

*Infections*—Acute and chronic infections may be associated with anemia and will therefore benefit by transfusion. In addition, fresh blood may contain antibacterial and antitoxic factors which aid in combating infection. In general, immunotransfusions have proved to be of little value although on occasions blood from carefully selected donors has appeared beneficial in the therapy of hemolytic streptococcus infections.

**TRANSFUSIONS FOR RED CELL DEFICIENCY**—*Anemia*.—Transfusion is of great value in the treatment of anemia in that it increases the number of red cells and thus increases the oxygen carrying capacity of the blood.<sup>7</sup> In many instances of sudden severe anemia due either to hemorrhage, hemolysis or bone marrow inhibition, transfusion is often a life-saving procedure. In some of the more chronic forms of anemia, transfusion should be used symptomatically for relief of symptoms, dangerously low hemoglobin, pre- and postoperative care and general support when necessary, while more specific remedial measures are being carried out.

**TRANSFUSION FOR WHITE CELL DEFICIENCY**—Transfusion has been used in the treatment of agranulocytosis, but its value is only that of a supportive measure. The life of the granulocytes is so short and the numbers infused are so small that transfusion has not proved to be of any clear-cut value in raising the white count.

**TRANSFUSION FOR PLATELET DEFICIENCY**—Thrombocytopenic purpura attended by significant hemorrhage, anemia or bleeding in a vital area constitutes an indication for transfusion. Since the platelets are rapidly destroyed when blood is stored, fresh blood should be used in these cases.

**TRANSFUSION FOR HEMORRHAGIC DISEASES**—The value of various specific components in the therapeutic arrest of hemorrhage in hemophilia and bleeding due to hypoprothrombinemia is discussed later. Fresh whole blood may be used when plasma or specific fractions are not available in attempting to stop bleeding in hemophilia or hypoprothrombinemia.

**New Developments in Blood Transfusion**—**IMPORTANCE OF THE RH FACTOR**—It has been demonstrated<sup>8</sup> that about eighty-seven per cent of the general white population, irrespective of their blood groups, possess a factor (an agglutinin) in their red blood cells which has been called Rh. These individuals are referred to as being Rh-positive. The other 13 per cent who do not have this factor in their red blood cells are referred to as being Rh-negative. The Rh-negative individuals can form antibodies (anti-Rh agglutinins)<sup>9</sup> under two circumstances.

1 *When repeated transfusions of Rh-positive blood are given to Rh-negative individuals*. The first time such a transfusion is given there are no ill effects. However, the Rh-negative individual may become sensitized and begin to develop anti-Rh agglutinins. After repeated transfusions with Rh-positive blood, the titer of these agglutinins may become significant. Not all individuals will develop demonstrable anti-Rh under these conditions but the sensitized Rh-negative patient who does may suffer a hemolytic transfusion reaction on subsequent infusion of Rh-positive cells. Once such a reaction has occurred, all future Rh-positive transfusions are apt to produce increasing symptoms of hemolysis.

2 *When an Rh-negative woman bears repeated Rh-positive children, she may develop anti-Rh agglutinins*. Presumably this takes place because of a break in the placental barrier which allows Rh-positive cells from the fetus to enter the maternal circulation and sensitize her. Clinical manifestations of such isosensitization usually do not appear in the first pregnancy of Rh-negative women unless they were previously sensitized by an Rh-positive blood transfusion. After the anti-Rh agglutinins have been formed by the mother they may be transmitted back to the fetus to produce hemolytic anemia of the newborn (erythroblastosis foetalis) in her subsequent Rh-positive offspring. Actually, this phenomenon is seen in only one out of fifteen matings in which the mother is Rh-negative and the father Rh-positive.

**Practical Applications**—1 Whenever repeated transfusions are contemplated or a previous transfusion has been given, Rh typing should be done and only Rh-negative blood transfused into Rh-negative recipients.

2 Any time that a transfusion reaction occurs, the Rh factors in the recipient and donor must be investigated before another transfusion is given

3 Rh-negative blood must be used in transfusing a woman who has delivered a baby with erythroblastosis foetalis.

4 Rh-negative blood should be used in transfusing newborn infants suffering from erythroblastosis foetalis Rh-positive blood may be used after the infant is two weeks old

5 Rh typing should be carried out prior to transfusing any female who has not passed beyond the childbearing age. The technic employed has been well described<sup>10 11</sup>

**MEDIA PROVIDING LONGER LIFE ON STORAGE.**—Much progress has been made in preserving whole blood so that it can be used for considerable time after storage. Among the many solutions proposed, that of Loutit and Mollison,<sup>12</sup> has proved to be satisfactory

The formula now in general use follows

Sodium citrate U.S.P. ( $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$ )	1.33 gm.
Citric acid U.S.P. ( $\text{C}_6\text{H}_8\text{O}_7 \cdot \text{H}_2\text{O}$ )	0.47 gm
Dextrose U.S.P.	3.00 gm.
Water (pyrogen free) to make	100.00 cc.
25 cc. of this solution to be used for 100 cc of blood.	

If this mixture is kept continuously refrigerated at 6° C., the blood may be safely used twenty-one days after it has been taken. This acid citrate dextrose (A.C.D.) preservative solution has the following advantages (1) It is simple and easy to prepare. (2) It may be safely autoclaved (3) The blood dilution is negligible (4) It is a superior and satisfactory preservative of red cells for at least twenty-one days (5) It produces negligible in vitro hemolysis even after six weeks.

The only significant disadvantage of this solution is that, since the amount of citrate is relatively small the blood must be mixed very thoroughly when taken to avoid clotting Blood should either be filtered before administration or administered with a filter in the line.

**THE USE OF GROUP O ("UNIVERSAL DONOR") BLOOD**—Recently it has been shown that group O blood may be used without cross matching for universal donor purposes on a large scale with relatively few reactions.<sup>13</sup> However, some reactions will still occur The safety of such a procedure is greatly increased by adding A and B substances\* to neutralize the anti-A and anti B agglutinins, which occur in high titer in the bloods of certain group O subjects Such neutralized O blood produces no more or even fewer reactions than cross-matched blood of the same group as the recipient.<sup>14</sup>

**RESUSPENDED RED BLOOD CELLS**—With the increased use of plasma more attention has been paid to the therapeutic possibilities of the re-

These substances have been commercially prepared by The Eli Lilly Company

**TRANSFUSION FOR PLATELET DEFICIENCY**—Thrombocytopenic purpura attended by significant hemorrhage, anemia or bleeding in a vital area constitutes an indication for transfusion. Since the platelets are rapidly destroyed when blood is stored, fresh blood should be used in these cases.

**TRANSFUSION FOR HEMORRHAGIC DISEASES**—The value of various specific components in the therapeutic arrest of hemorrhage in hemophilia and bleeding due to hypoprothrombinemia is discussed later. Fresh whole blood may be used when plasma or specific fractions are not available in attempting to stop bleeding in hemophilia or hypoprothrombinemia.

**New Developments in Blood Transfusion**—**IMPORTANCE OF THE RH FACTOR**—It has been demonstrated<sup>8</sup> that about eighty-seven per cent of the general white population, irrespective of their blood groups, possess a factor (an agglutinin) in their red blood cells which has been called Rh. These individuals are referred to as being Rh-positive. The other 13 per cent who do not have this factor in their red blood cells are referred to as being Rh-negative. The Rh-negative individuals can form antibodies (anti-Rh agglutinins)<sup>9</sup> under two circumstances.

1 *When repeated transfusions of Rh-positive blood are given to Rh-negative individuals*. The first time such a transfusion is given there are no ill effects. However, the Rh-negative individual may become sensitized and begin to develop anti-Rh agglutinins. After repeated transfusions with Rh-positive blood, the titer of these agglutinins may become significant. Not all individuals will develop demonstrable anti-Rh under these conditions but the sensitized Rh-negative patient who does may suffer a hemolytic transfusion reaction on subsequent infusion of Rh-positive cells. Once such a reaction has occurred, all future Rh-positive transfusions are apt to produce increasing symptoms of hemolysis.

2 *When an Rh-negative woman bears repeated Rh-positive children, she may develop anti-Rh agglutinins*. Presumably this takes place because of a break in the placental barrier which allows Rh-positive cells from the fetus to enter the maternal circulation and sensitize her. Clinical manifestations of such isoimmunization usually do not appear in the first pregnancy of Rh-negative women unless they were previously sensitized by an Rh-positive blood transfusion. After the anti-Rh agglutinins have been formed by the mother they may be transmitted back to the fetus to produce hemolytic anemia of the newborn (erythroblastosis foetalis) in her subsequent Rh-positive offspring. Actually, this phenomenon is seen in only one out of fifteen matings in which the mother is Rh-negative and the father Rh-positive.

**Practical Applications**—1 Whenever repeated transfusions are contemplated or a previous transfusion has been given, Rh typing should be done and only Rh-negative blood transfused into Rh-negative recipients.

2 Any time that a transfusion reaction occurs, the Rh factors in the recipient and donor must be investigated before another transfusion is given

3 Rh negative blood must be used in transfusing a woman who has delivered a baby with erythroblastosis foetalis

4 Rh negative blood should be used in transfusing newborn infants suffering from erythroblastosis foetalis Rh-positive blood may be used after the infant is two weeks old

5 Rh typing should be carried out prior to transfusing any female who has not passed beyond the childbearing age The technic employed has been well described<sup>10 11</sup>

**MEDIA PROVIDING LONGER LIFE ON STORAGE.**—Much progress has been made in preserving whole blood so that it can be used for considerable time after storage. Among the many solutions proposed, that of Loutit and Mollison,<sup>12</sup> has proved to be satisfactory

The formula now in general use follows

Sodium citrate U.S.P. ( $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7 \cdot 2\text{H}_2\text{O}$ )	1.33 gm.
Citric acid U.S.P. ( $\text{C}_6\text{H}_8\text{O}_7 \cdot \text{H}_2\text{O}$ )	0.47 gm.
Dextrose U.S.P.	3.00 gm.
Water (pyrogen-free) to make	100.00 cc.
25 cc. of this solution to be used for 100 cc. of blood.	

If this mixture is kept continuously refrigerated at 6° C., the blood may be safely used twenty-one days after it has been taken. This acid citrate dextrose (A.C.D.) preservative solution has the following advantages: (1) It is simple and easy to prepare. (2) It may be safely autoclaved. (3) The blood dilution is negligible. (4) It is a superior and satisfactory preservative of red cells for at least twenty-one days. (5) It produces negligible in vitro hemolysis even after six weeks.

The only significant disadvantage of this solution is that, since the amount of citrate is relatively small, the blood must be mixed very thoroughly when taken to avoid clotting. Blood should either be filtered before administration or administered with a filter in the line.

**THE USE OF GROUP O ("UNIVERSAL DONOR") BLOOD.**—Recently it has been shown that group O blood may be used without cross matching for universal donor purposes on a large scale with relatively few reactions.<sup>13</sup> However, some reactions will still occur. The safety of such a procedure is greatly increased by adding A and B substances\* to neutralize the anti-A and anti-B agglutinins which occur in high titer in the bloods of certain group O subjects. Such neutralized O blood produces no more or even fewer reactions than cross-matched blood of the same group as the recipient.<sup>14</sup>

**RESUSPENDED RED BLOOD CELLS.**—With the increased use of plasma more attention has been paid to the therapeutic possibilities of the re-

\* These substances have been commercially prepared by The Eli Lilly Company



maining red cells<sup>15 16</sup> The use of these cells offers the advantage of the economy of using all the constituents of blood as well as providing a method of administering larger amounts of red blood cells with less of an increase in blood volume than if whole blood were used The chief indications for its use are the anemias It is of special value in anemia with cardiac insufficiency where it is desirable to add red cells without increasing the blood volume and hence increasing the load on the heart It is also indicated when red cells are needed by any individual with a relatively normal blood volume The use of resuspended red blood cells is contraindicated in shock, hemoconcentration, burns and hypoproteinemia, unless plasma or albumin are also administered to provide the needed plasma protein

The method employed at the moment is to centrifuge the whole blood, remove the plasma and resuspend the red cells in pyrogen-free isotonic saline This should be stored at 4° to 10° C and discarded if any freezing occurs Scrupulously sterile technic must be employed and if a purplish or black-red color or unusual odor appears the suspension must not be used When once opened for use, any remaining suspension ought to be discarded The suspension should not be warmed and must be filtered carefully before use, or administered through a suitable filter

It is best to use these cells within twenty-four hours after bleeding as their life duration in saline suspension is short, although they have been used up to five days If the cells are packed and resuspended in a relatively small amount of saline they are more fragile The use of resuspended cells is probably only in its infancy There is need for a more satisfactory diluent than saline so as to prolong the effective life of the cells to three to four weeks Under these circumstances the suspension could be held long enough for the completion of sterility tests, and thus would probably diminish the chances of transferring diseases such as malaria and syphilis, the agents of which die on storage in the cold for more than a few days

**Blood Grouping Technic**—Hemolytic transfusion reactions are almost always due to agglutination of the donor's cells by the recipient's plasma With the increased use of group O blood, there has been a tendency to omit preliminary cross matching before transfusion since the donor cells are inagglutinable in any plasma This practice is justifiable *provided the technic used for grouping the donors is above reproach* In using A or B or AB cells where the donor's cells contain agglutinin, reactions may occur if there has been a mistake in grouping either donor or recipient and thus cross matching should always be done before transfusion As has been pointed out above, Rh-negative blood or cells only must be used in certain situations Table 5 shows the standard international blood group classification, which has properly replaced the Moss and Jansky classifications

*Blood grouping serum must be of high potency and high avidity for*

satisfactory grouping,\* since  $A_2B$  and  $A_2$  cells may be so weakly agglutinable that they are missed and classed as B cells and O cells respectively. Good serum may be obtained from a number of sources. As a result of the plasma fractionation program, isoagglutinins have been concentrated for the armed forces from the plasma of grouped bloods, yielding a product of high potency which has proved very satisfactory.<sup>17 18</sup> These preparations are usually issued in the dry state to preserve potency and are reconstituted just before use. Certain

TABLE 5—BLOOD GROUPS  
(International Classification)

	Agglutination of Subject's Cells by Known Serum		Agglutination of Known Cells by Subject's Serum	
	A Serum (anti B)	B Serum (anti A)	A Cells	B Cells
Group O (Universal donor) (Moss IV) (Jansky I)	0	0	+	+
Group A (Moss II) (Jansky II)	0	+	0	+
Group B (Moss III) (Jansky III)	+	0	+	0
Group AB (Universal recipient) (Moss I) (Jansky IV)	+	+	0	

hospitals bleed professional donors for serum. This practice is not justifiable if the serum is standardized against the weakly agglutinable cells of an  $A_2B$  donor to be sure it has adequate potency and if a given lot is retested at intervals. Storage of serum at room temperature or the use of contaminated serum is absolutely contraindicated.

### III USE OF PLASMA OR SERUM

Properties of Different Forms of Plasma and Serum.—Plasma or serum may be used interchangeably in most circumstances, although the latter lacks the fibrinogen, which may occasionally be needed. The British and Canadians have used pooled serum extensively in this war as it does away with the necessity for centrifugation and may be sterilized by Seitz filtration. Their experience indicates that there is little in fact for the old idea that serum gives rise to more reactions than plasma.<sup>19</sup>

\* Satisfactory serum may be prepared in various commercial laboratories.

plasma Plasma has the advantage that the red cells can be salvaged, and the separation between plasma and cells can be made promptly by centrifugation Plasma may be salvaged from bank blood, which has been stored too long for use as such, but will have an appreciable content of hemoglobin and potassium and a low content of labile constituents such as prothrombin Either plasma or serum should be pooled in lots derived from at least twelve donors This lowers the isoagglutinin content markedly, and avoids the danger of destruction of the recipient's cells which might occur if a large dose of plasma with a high isoagglutinin titer for his cells were used Pooled plasma can be given in large amounts without preliminary cross matching Its sterility should be checked and serologic tests for syphilis made on the individual bloods before release for clinical use

TABLE 6—FORMS OF PLASMA AND SERUM

Form	Storage	Preparation for Use	Colloid Osmotic Pressure	Nutrition	Prothrombin	Fibrinogen	Hemophilic Globulin	Antibodies
<i>Liquid Plasma Serum</i>	Room temp Sterility must be proved	None	+	+	0 0	0 0	0 0	0(1) 0(1)
<i>Frozen Plasma Serum</i>	-10° C for months	Thaw at 37° C	+	+	+	+	+	+
<i>Dried Plasma Serum</i>	Any natural temp for year Use in 2-3 hrs.	Reconstitute with water	+	+	0 0	+	+	+

(1) Antibodies preserved for a number of months if stored at ice box temperatures.

Plasma or serum can be stored for use in several forms Since these forms differ in their content of various functionally important constituents, the physician should be familiar with the properties of each These are listed in Table 6 In the administration of plasma or serum in any form, as with whole blood or resuspended cells, the *inclusion of a suitable filter in the tubing through which the fluid is administered is imperative* to exclude particulate matter

Liquid plasma has the great advantage of being capable of storage without refrigeration and of being available for immediate administration to patients in shock, where speed is essential<sup>19, 20</sup> It provides the needed colloid, but other functional constituents are lacking for the most part<sup>21</sup> The labile components are best preserved in frozen plasma<sup>22</sup> It must be thawed before use, which takes time Dried plasma must be reconstituted before use, which requires several minutes and means that the package must contain a bottle of sterile pyrogen-free water as well as the bottle of dried plasma It can be shipped and stored under almost any conditions with a fair degree of preservation

of those labile constituents present when the drying was carried out, except prothrombin.<sup>23</sup>

**Indications—Loss of PLASMA**—This occurs at a rapid rate into the injured area in cases of *burns, severe trauma, and peritoneal irritation*. Evidence for the general leakage of plasma through all the capillaries of the body, which has been postulated as characteristic of advanced surgical shock, is lacking. Probably it does occur through the pulmonary capillaries in cases of blast, poison gas, and thermal injuries of the lungs, and in severe pulmonary infections (influenzal pneumonia) and throughout the body in cases of anaphylactic shock and overwhelming infection.

The loss of plasma can be detected by a rising value for the hematocrit, hemoglobin or whole blood specific gravity without a corresponding rise in plasma proteins such as occurs in dehydration. An attempt should be made to keep this value near normal (see Fig 161) by administration of plasma or 5 per cent albumin in saline.

The treatment of shock due to loss of plasma as in burns or peritonitis requires constant attention to a number of details. Once the shock phase is passed, nutritional problems become all-important.<sup>24 25</sup> Table 4 lists most of the important clinical and laboratory observations which can be used to guide the course of treatment. Special attention should be given to the following:

1 *The state of the peripheral circulation*. A low blood pressure, rapid pulse rate, and poor quality pulse indicates inadequate replacement, and the rate of fluid replacement should be speeded up.

2 *The urine output*. In shock of any type urine output falls markedly as a result of the poor renal circulation. It is vital to administer sufficient water by mouth or glucose solution by vein to provide water for excretion, sufficient salt to keep the volume of extracellular fluid near normal, and sufficient colloid to keep the blood pressure at a point where adequate glomerular filtration occurs. The urine output and nonprotein nitrogen (or blood urea nitrogen) should be followed closely.

3 *The plasma proteins* (specific gravity measurements satisfactory). Enormous losses of plasma occur in the early phases, while there is a tremendous increase in the rate of protein breakdown which persists for a long period after the injury. Consequently it is extremely difficult to keep the level of serum proteins above the edema level. In the first few days of treatment of a burn case huge amounts of plasma may be necessary to sustain the plasma specific gravity. A working formula for the administration of plasma is 100 cc. of plasma for every point the hematocrit reading exceeds the normal of 45 in an average sized adult. For children the dose should be scaled down proportionately.

Thereafter plasma should be given as needed to keep the whole blood specific gravity down near normal, the peripheral circulation satisfactory, and the plasma specific gravity near normal. Large

amounts of fluid with salt or sodium lactate should be given by mouth as tolerated and supplemented by saline and glucose by vein as needed to maintain a good urine output. Excessive intravenous saline or glucose will produce a lowering of the plasma proteins and a return of the shock picture. Food should be given in as large amounts as can be tolerated in an effort to combat the wasting of body proteins. The diet should supply a liberal quantity of protein and calories and a generous supply of all the vitamins.

4 *The red cells* Blood should be given frequently in an effort to sustain the hemoglobin level.

5 *Infection* Infection of the traumatized area almost invariably occurs in burns as in war wounds and hence chemotherapy and local surgical treatment are of great importance.<sup>20</sup> Infection probably contributes markedly to the development of anemia and hypoproteinemia.

**SURGICAL SHOCK**—The major component of surgical shock due to trauma or operation is hemorrhage. Whole blood is the treatment of choice, but plasma or albumin should be used to supply the colloid needed to maintain an adequate circulation while blood is being obtained for transfusion. In these cases, plasma or albumin restores the blood volume but the patient develops an anemia, which should be corrected as soon as possible to promote optimal recovery. Five hundred to 1500 cc of plasma (or 25 to 75 gm of albumin) are quite effective in these cases, but no more than 1500 cc of plasma should be given without blood unless none of the latter is available. It is worth emphasizing that, in severe trauma, it is best to treat the patient promptly and if possible before clinical shock is evident.

**MEDICAL SHOCK**—Peripheral vascular collapse, as manifested by low blood pressure, weak thready pulse, cold, clammy extremities, pallor, anxiety and restlessness, occurs in a wide variety of conditions. Its intelligent treatment demands recognition of the causative factors. Where cardiac disease—acute myocardial failure after a coronary occlusion or cardiac tamponade developing from acute pericarditis—is the chief factor, therapy must be directed at the heart. Where metabolic disorders are the chief cause—the hypoglycemia of insulin shock or hypoadrenalism, the loss of electrolytes characteristic of diabetic coma or Addison's disease—not only is repair of the chemical deficit required (glucose or sodium chloride) but also replacement with the proper hormone. It is in severe infections such as scarlet fever, meningococcus meningitis, typhus fever and ulcerative colitis that the picture of shock is most often seen. Here multiple factors may be operative: (1) reduction in blood volume from loss of plasma through damaged capillaries or from loss of electrolytes by vomiting, diarrhea or sweating, (2) increase in capacity of the vascular system from loss of vasomotor tone, (3) hypoproteinemia, (4) anemia, (5) hyperpyrexia, and (6) acute adrenal insufficiency as a result of massive hemorrhage into the adrenal glands in the rare instance of Waterhouse-Friderichsen syndrome. Control of the infectious process by intensive

chemotherapy and antitoxic therapy (convalescent serum or antitoxin in scarlet fever and antitoxin in diphtheria) is the most essential phase of treatment. However, supportive therapy may tide a patient over the period before specific measures against the infection become effective in reducing the "toxemia," while in diseases such as Rocky Mountain spotted fever<sup>27a</sup> or ulcerative colitis, for which there is no specific treatment, it may make the difference between life and death.

Supportive therapy should include oxygen for anoxia, saline (preferably given subcutaneously) for dehydration, glucose, vitamins and amino acids for nutritional purposes, adrenal cortical extract and desoxycorticosterone supplemented with saline and glucose if low blood pressure and collapse appear in a patient with widespread purpura,<sup>27b</sup> blood for anemia, and plasma for shock and hypoproteinemia. Two hundred to 500 cc of plasma may be life-saving in the first few hours of a severe septic infection before penicillin or sulfonamides have exerted their antibacterial effect. A word of caution should be interjected at this point. In severe pulmonary infections, particularly interstitial pneumonia and particularly in infants and small children, the overenthusiastic use of intravenous fluids of any type is apt to produce pulmonary edema and thus to exaggerate the anoxia already present.

**DEFICIENCIES OF SPECIFIC PLASMA PROTEINS—HYPOPROTEINEMIA.**—In actual fact, *hypoproteinemia is usually hypoalbuminemia*,<sup>28</sup> so that its correction involves restoration of the serum albumin level toward normal. For this purpose albumin should obviously be superior to plasma, but although this product of plasma fractionation has been given considerable clinical trial, so far it has been available only for the armed forces. Since the indications for and uses of plasma and albumin are essentially the same in treating hypoproteinemia, these will be discussed together. Until albumin becomes more available, plasma will have to be used in such cases.

The chief clinical manifestation of hypoalbuminemia is edema, although the serum albumin level may be below optimum before this is grossly manifest. Edema may be due to fluid retained in the tissues because of increased retention of salt, or because of lowered osmotic pressure of the blood, or from the activity of both of these factors. The giving of plasma or albumin alone may not suffice to correct hypoproteinemia and edema in certain cases. One should determine the cause of the lowered serum protein level.

**CAUSES OF HYPOPROTEINEMIA** 1 **Inadequate Protein Intake**—Since food is the natural source of proteins that can be assimilated for the body's use, conditions such as prolonged anorexia, dietary idiosyncrasies, and starvation may be important factors in lowering the protein supply. In these cases serum albumin is utilized to meet the demands of the body, with a resulting gradual fall in its concentration in the plasma. Starvation per se results in a lowering of the metabolic rate, and a more or less diffuse destruction of body protein so that hypoproteinemia is rarely conspicuous. On the other hand, if a patient

eats a relatively small amount of protein in relation to the total caloric intake, hypoproteinemia develops more rapidly

2 **Excessive Protein Loss**—*Loss of protein from the body* occurs in the urine in the nephrotic syndrome, in the fluids removed by paracentesis of rapidly recurring effusions in the serous cavities and in the oozing of plasma from burns, wounds, or skin lesions such as eczema

*Increased destruction of body proteins* occurs in infections, burns, and after operations or injuries when the catabolic activities may be so greatly enhanced that it is almost impossible to achieve nitrogen balance with any but enormous amounts of protein. As our methods for the treatment of serious infections and burns improve, the nutritional requirements of convalescence assume increasing importance.<sup>20</sup>

3 **Defects of Protein Metabolism**—*Poor absorption* may be responsible. In certain gastrointestinal diseases such as pancreatic insufficiency or diarrheal disease the amount of hydrolyzed protein absorbed from the bowel may be diminished because of lack of proper enzymes or too rapid passage through the gut. The administration of hydrolyzed protein (amino acids) by mouth makes it possible to obtain a positive nitrogen balance in many of these cases.<sup>30</sup>

*Impaired synthesis* is sometimes present. In hepatic disease the organ which manufactures serum albumin is involved. Thus a low serum albumin level may be one of the signs of hepatic failure and is observed in cases of acute hepatitis and particularly in cirrhosis of the liver.<sup>31</sup>

**CORRECTION OF HYPOPROTEINEMIA**—In the treatment of hypoproteinemia, the administration of very much larger amounts of protein is necessary than would be expected on the basis of the deficit in total circulating protein. Most of the administered protein is apparently stored in the tissues. In hypoalbuminemic dogs fed a very high protein diet, Elman<sup>32</sup> has shown that only one-thirtieth of the protein fed could be accounted for by the increase of circulating albumin. Obviously the correction of hypoproteinemia can be most economically achieved by stimulation therapy—namely, a high protein, high caloric diet, sometimes supplemented by amino acids and glucose administered either parenterally or orally. Unfortunately this takes time and the situation may demand rapid correction. Moreover, in the face of the increased breakdown of body protein occurring in infections and after injuries or in hepatic failure this may be ineffectual. Thus parenteral protein feeding has to be used frequently and plasma must be given by slow drip in doses of from 500 to 1000 cc per day. If used, it should be supplemented in a patient who cannot take oral feeding by as many calories in the form of glucose as possible, and by injection of sufficient doses of vitamin B complex and vitamin C to insure good carbohydrate utilization, in the patient who can eat, a very large intake of protein with carbohydrate will increase the effectiveness of the injected plasma by sparing the body proteins.

The remaining plasma proteins that, by their absence, may give rise to specific deficiencies, can also be replaced by giving plasma in the proper form. As indicated in Table 3, frozen plasma contains most of the active components besides the albumin—this is also true of fresh plasma or blood. The components fall into two main groups: the globulins associated with blood coagulation and those associated with immunity.

**Prothrombin Deficiency**—The administration of vitamin K orally with bile salts or by injection will usually result in a rapid rise in prothrombin time to normal. In certain instances of severe hepatic damage (hepatitis, salicylate or dicoumarol poisoning), this will not be effective and prothrombin should be supplied by frozen or fresh plasma or fresh blood.

**Hemophilia**—The primary defect in hemophilia appears to be lack of a globulin which accelerates the clotting of hemophilic blood both *in vitro* and *in vivo*. This globulin is quite labile and therefore fresh blood or fresh or frozen plasma (50 to 100 cc. doses) must be used and repeated doses must be given at critical times so as to keep the clotting time near normal. Because the hemophilic globulin is but a small fraction of the total plasma proteins, undesirable side effects from the large amounts of blood and plasma necessary may occur. It is to be hoped that a plasma fraction will be prepared that may provide the active globulin for injection in a small volume.<sup>33</sup>

**Fibrinogen Deficiency**—This rarely occurs except in overwhelming liver damage as in acute yellow atrophy. The prognosis from the disease itself is so poor that repair of the defect in blood coagulation, although it should be attempted with frozen or dried plasma, probably has little to offer the patient.

**Convalescent and Hyperimmune Serum and Plasma**—The use of human immune bodies in the treatment and prevention of disease has become common practice in recent years.<sup>34</sup> A list of the conditions where there is some evidence for their effectiveness follows.

Disease	Agent	Objective	Dose	Results
Measles	Pooled adult serum	Prevention or Modification	10- 30 cc.	Fair
Scarlet fever	Convalescent serum	Treatment	5- 20 cc.	Excellent
	Pooled adult serum		250-500 cc.	Fair
Mumps	Convalescent serum	Prevention	50-100 cc.	Good
	Convalescent serum		10- 20 cc.	Questionable
Pertussis	Hyperimmune serum*	Prevention	10- 20 cc.	Excellent
		Treatment	60- 80 cc.	Good

\* Hyperimmune pertussis serum may be obtained from the Philadelphia Convalescent Serum Exchange, 1740 Bainbridge Street, Philadelphia, Pennsylvania. A globulin concentrate containing the antibody fraction of such serum is marketed by The Cutter Laboratories, Berkeley, California, under the name of Hypertussis. Other types of human convalescent sera can usually be obtained from various serum centers.



## IV USE OF PRODUCTS OF PLASMA FRACTIONATION

It is suggested from the above discussion that since whole blood and plasma have specific indications for therapy in a wide variety of conditions, the individual components would be even more valuable in isolated form. The products of plasma fractionation<sup>35</sup> have been given considerable clinical trial, but so far have been available only to the armed forces, except for immune serum globulin.

**Human Serum Albumin**—This is distributed in 100 cc bottles containing 25 gm of albumin which is equivalent in osmotic effect to 500 cc of citrated plasma. Albumin solution has contained in the past approximately twice the isotonic concentration of sodium chloride, but interest in its use as a physiological diuretic agent has led to the development of a solution of much lower salt content.<sup>36</sup> Besides the great conveniences of a small compact package, ready for use without reconstitution or cross matching, and the safety and ease with which it can be administered, albumin has the great advantage that it can be combined in any desired concentration with any of the solutions used parenterally. Five per cent albumin in saline solution is approximately isotonic with plasma and can be used interchangeably with it in the treatment of burns.

Indications for the use of albumin are as follows:

**Shock**—Albumin provides effective colloid osmotic pressure for the emergency treatment of traumatic shock. It increases blood volume by drawing water from the tissues into the circulation, and in severely dehydrated patients additional saline should be provided for the relief of dehydration.

**Hypoproteinemia**—In this condition it is the logical solution for replacement therapy, since it provides the maximum amount of protein with a minimum amount of fluid and no extra salt. Thus, rapid increase in the colloid osmotic pressure with mobilization of water from the edematous tissues can be achieved, by the injection of small amounts of material, a particular advantage in pediatric practice. The low salt content of the solution is of importance in the treatment of edematous patients with renal disease.<sup>37</sup>

**Proteins Concerned in Blood Coagulation and Their Derivatives**—The formation of a blood clot is the result of a complicated series of chemical reactions. Since we can now isolate some of the substances involved in this mechanism, however, it is possible to "arrest" the process at various stages and use the intermediate products. Thus, prothrombin can be combined with thromboplastin for the formation of thrombin. If this is done quantitatively with a known amount of thromboplastin and a blood of unknown prothrombin content, the concentration of the latter can be determined by the length of time it takes the clot to form—the "prothrombin time." Thrombin itself has found many uses, particularly in the field of surgery. Combined with fibrinogen, it

forms the fibrin which is the meshwork of the blood clot. The conditions under which these two substances are allowed to combine (relative amounts, thickness of mold, drying conditions, etc.), determine the form the fibrin product will take. We have therefore fibrin foam, fibrin film, and other products which may be developed in much the same way as new "plastics" are developed in industry. *Fibrin foam* has wide clinical application in hemostasis. As a base for *thrombin*, it may be dipped in a solution of the latter, applied to a bleeding point and left in place after it has stopped the bleeding, to be reabsorbed as healing takes place. It is particularly useful in neurosurgery, as is *fibrin film*—a sheet-like preparation of fibrinogen plus thrombin with rubbery tensile strength—which may be used as a dural substitute. These substances cause no local irritative reaction. Thrombin itself, or "clotting globulin," has also been obtained from rabbit plasma and is extremely useful in controlling localized external bleeding in hemophiliacs when applied with pressure, particularly in powder form.\* Another ingenious use of fibrinogen and thrombin is to inject solutions of these substances separately into the pelvis of a kidney that contains calculi. As the clot forms, a "cast" of the renal pelvis is made, enmeshing the stones so that they are removed with removal of the whole clot. Finally, a film of fibrinogen and thrombin may be useful in the local treatment of denuded areas and burns, especially when such lesions must be protected while the patient is being transported to a place where more extensive therapy can be carried out.

**Immune Serum Globulin (Gamma Globulin)**—The gamma globulin fraction of pooled human plasma has been shown to contain the antibodies that reflect the immunity status of the donors. By separation of this gamma globulin fraction these antibodies can be concentrated approximately twenty-five times over the starting material, so that it is possible to give the equivalent of 125 cc. of pooled normal serum by the intramuscular injection of 5 cc. of globulin. This fraction theoretically should be able to confer passive immunity for protection of susceptible persons against diseases to which adults have a lasting immunity of a humoral type. Likewise, the gamma globulin derived from normal convalescent or hyperimmune blood should be valuable in the treatment of those diseases in which the corresponding sera are known to be of value.

Immune serum globulin (human) (gamma globulin antibodies) has been prepared in large amounts from the blood collected from normal adults by the American Red Cross. Because the production of human serum albumin for the armed forces has made available more gamma globulin than is needed by these services, arrangements have been made by the American Red Cross for the distribution of excess globulin for civilian use through local health departments.

*Immune serum globulin* should be distinguished from *immune globulin*—"Hemostatic globulin," prepared commercially by Lederle Laboratories.

*bulin* prepared from human placentas since it is more potent, better standardized, and gives rise to very few reactions<sup>38</sup>

The prophylactic use of gamma globulin has been proved for two diseases—measles and infectious hepatitis (epidemic "catarrhal" jaundice)<sup>39</sup> The results of available studies on its use are tabulated below

Disease	Given after Exposure, before Symptoms Appear		Treatment after Symptoms Appear
	Prevention	Modification	
Measles	+ (Dose 0.1 cc per lb in first 6 days)	+ (Dose 0.025 cc per lb in first 6 days)	Some effect if given in large dose before rash appears
Infectious hepatitis	+ (Dose 0.1 cc per lb)	Under investigation	Under investigation
Mumps	0	0	0
Chickenpox	0	0	—

Key +, proved effective  
0, proved ineffective  
—, no studies made

The globulin is injected intramuscularly and in the usual doses causes very little or no local reaction and only rarely mild general symptoms, principally slight fever. It should not be used intravenously. Its most important civilian use is in the prevention of measles after exposure in sick or debilitated children or in the attenuation of the disease in healthy susceptible contacts. The mild disease carries a much lower risk of complications and probably gives rise to permanent immunity, though this has not been proved. Such passive immunization is effective for about three weeks and must be repeated after that interval if the patient is reexposed. Recognition of the mild disease may not always be easy. Fever, malaise and catarrhal symptoms are usually markedly diminished in intensity and duration. The rash may be sparse and transient. The incubation period may appear to be prolonged since the prodromal stage is largely eliminated.

#### V REACTIONS FOLLOWING INTRAVENOUS ADMINISTRATION OF BLOOD OR ITS DERIVATIVES

The intravenous administration of whole blood, resuspended red blood cells, plasma, or albumin, while relatively safe, may at times be associated with reactions of different types and varying severity. No preparation of gamma globulin suitable for intravenous use has as yet

been prepared and this material should only be employed intramuscularly. The various types of reactions noted are discussed below.

**Reactions Due to Physical Causes ("Speed" Reactions).—**For the most part, this type of reaction is produced by an excessively rapid rate of infusion. It is unusual to see this type when albumin is employed. The symptoms produced are primarily those of pulmonary edema and cardiac embarrassment or insufficiency. The best treatment is prophylactic employment of a slow rate of injection. If a reaction of this variety is noted, the infusion must be stopped immediately and symptomatic care given.

**Reactions Due to Chemical Agents ("Pyrogen" Reactions).—**This type of reaction is produced by chemical or bacterial contamination of the fluids administered. Such contamination is most apt to take place in the final handling, the transfusion equipment or the fluids used to fill the circuit before adding the solution to be infused. Within ten to sixty minutes the recipient develops high fever (often up to  $105^{\circ}$ ) and severe shaking chills, which may last for a few minutes or several hours. Prophylactic treatment should be directed toward preventing such reactions by the use of pyrogen-free solutions and equipment. Once such a reaction takes place it is advisable to keep the patient covered with blankets during the shaking chill and then employ antipyretic measures such as rectal taps of cold water, alcohol sponges and salicylate therapy. Aspirin may be given in repeated doses of 0.3 gm. to infants, 0.6 gm. to children and 1.0 gm. to adults. Sodium salicylate may be administered intravenously in the same doses if more rapid results are desirable or if the drug is refused orally.

**Reactions Due to Allergic and Anaphylactic Phenomena.—**Reactions of this type are seen primarily with the transfusion of whole blood and plasma and are unusual when resuspended red cells or albumin are used. The reactions are due to the presence in the donor's blood of some antigen to which the recipient is sensitive or of some antibody reacting with an antigen present in the recipient's circulation. It results in sneezing, epiphora, urticaria and asthma in the mild cases. The more severe reactions may be attended by dyspnea, cyanosis and collapse. Such reactions are best prevented by using only fasting donors and excluding those who are highly allergic or have recently received vaccines or foreign serum. If difficulty is anticipated in an allergic recipient, a skin test may be performed using 0.1 cc. intradermally of a 1:20 saline dilution of the donor plasma or serum prior to the transfusion. Once such a reaction occurs, it should be treated by the subcutaneous or intravenous injection of 0.5 cc. of 1:1000 adrenalin.

**Disease Transmission.—**The possibility exists that many diseases could be transmitted from donor to recipient. Actually this happens only rarely. The most important diseases transmitted by transfusions of blood or its derivatives are syphilis, malaria (particularly quartan) and hepatitis (homologous serum jaundice). The symptoms are of course

those of the disease imparted. Treatment should be directed towards screening out diseased donors by a careful history, physical examination and routine serology. The problem of the transmission of homologous serum jaundice has received a great deal of attention recently,<sup>40</sup> but so far no satisfactory method of dealing with this problem has been devised. Recipients of icterogenic blood or plasma usually develop jaundice two to six months after receiving the transfusion, and the resulting hepatitis may vary from a severe and even fatal disease to one in which symptoms would not be recognized as of hepatic origin without laboratory studies.<sup>41</sup>

**Hemolytic Reactions (Due to Blood Incompatibility)**—These reactions, since they are usually due either to mismatching or Rh incompatibilities, are seen only with the use of whole blood, resuspended red cells, or nonpooled plasma. The reaction most often occurs after a relatively small amount of blood is injected but may at times be delayed until after a full transfusion depending on the strength of the agglutinin and its speed of action. It is wise to avoid transfusing anesthetized individuals, whenever possible, for fear of masking such a reaction. The recipient who is experiencing such a hemolytic transfusion reaction becomes restless and anxious. He often complains of pain especially over the kidney regions. This pain at times is excruciating. Chills and fever, dyspnea, vomiting and collapse may soon follow. Hemoglobinuria, oliguria and even anuria are fairly common. Later icterus appears with anemia. Uremia may be present if renal shutdown is prolonged.

Again the best prophylaxis is careful blood grouping and cross matching as discussed previously. Specific therapy is directed towards

1 Alkalinizing the urine in an effort to free any acid hematin precipitated in the kidney and establishing a flow of urine in oliguric or anuric individuals. The measures commonly employed include intravenous one-sixth molar sodium lactate in doses of 500 to 1000 cc in adults and 10 cc/lb of body weight in infants and children, intravenous sodium bicarbonate either as an isotonic solution (1.5 per cent) or hypertonic solutions of 3 to 6 per cent. The oral administration of sodium bicarbonate requires dosages of 15 gm per day in adults with the obvious drawbacks of the slow action of oral doses and the difficulty of vomiting when such high doses are employed.

If oliguria is marked or anuria is present, the decision as to the amounts and types of fluids to be administered should be guided by chemical and clinical observations. An attempt should be made to provide sufficient fluid to keep water available for excretion but not to flood the patient with water in such quantities as to seriously lower the concentrations of electrolytes in extracellular fluid.

2 Correcting the resulting anemia by the transfusion of fresh compatible blood.

3 Maintaining the patient with general supportive therapy.

## VI BLOOD SUBSTITUTES

Blood substitutes are of two types, those derived from natural sources and those from unnatural ones.

**Blood Substitutes from Natural Sources**—I **PLASMA PROTEINS FROM OTHER ANIMAL SPECIES**—Since the plasma proteins of different species resemble one another in their physicochemical properties, although differing markedly on an immunological basis, it is natural that one should turn to them as representing the molecules most likely to function physiologically in the human body. The primary difficulty in the therapeutic use of heterologous plasma proteins is that they are usually antigenic, giving rise to delayed reactions of the serum sickness types, and frequently contain antibodies to human cells which give rise to immediate reactions. Nevertheless considerable work has been done upon this problem.

**Bovine Plasma.**—Wangensteen and his colleagues have shown that the injection of unmodified bovine plasma is attended with a high incidence of immediate and delayed reactions, although the proteins can apparently be utilized in metabolism.

**Bovine Albumin.**—In an effort to get rid of the immediate reactions, a number of workers have attempted to purify the albumin fraction of bovine plasma with considerable success. Other albumins have likewise been used. No published evidence is available on the ultimate safety of these solutions in man.

**Despecciated Bovine Serum.**—In an effort to overcome the immediate reactions, Edwards in England has been using a combination of heat and formalin to treat bovine serum. Such treatment has apparently yielded a product which gives rise to few if any immediate or delayed reactions and in which the osmotic properties of the protein, although damaged, are not completely destroyed.

**GELATIN AND ITS DERIVATIVES**—*Gelatin* has been proposed. Its colloid osmotic pressure, however, is chiefly due to small molecules which are rapidly lost from the circulation while the large molecules which are long and slender have little osmotic effect but marked effect upon blood viscosity and the sedimentation rate. Furthermore, gelatin is an incomplete protein from the nutritional standpoint. *Isinglass* or *fish gelatin* has likewise been proposed and although possibly slightly superior to animal gelatin in physical properties suffers from the same general defects. *Oxypolygel* represents an attempt by chemical manipulation to overcome the inherent defects of the long thin gelatin molecule. Little data on this substance is available. The chief asset of all the gelatin derivatives is that they are, at least, nonantigenic.

**Blood Substitutes from Unnatural Sources.**—*Gum acacia* was introduced in the last war. Its great defect for repeated injection is that it drives

\* The following paragraphs are merely intended as a brief survey of this field. The results of the search for a satisfactory blood substitute do not justify a complete discussion.

the plasma proteins from the circulation and also is slowly deposited in the liver, thus interfering with protein synthesis and ultimately defeating its own ends

*Pectin* has also been proposed and would appear to suffer from the defects of acacia but very little is known about its ultimate fate

This list could be expanded considerably. So far no blood substitute which fulfills the criteria for a satisfactory therapeutic agent has been discovered, and as long as there is an adequate supply of human blood, plasma and plasma protein fractions, it will be surprising if any substitute can be found to do the job as well as the molecules developed by the process of evolution.

## VII SUMMARY

An attempt has been made to summarize the basic knowledge in a very large field of therapeutics. No physician or surgeon can afford not to understand the fundamental principles underlying the proper use of blood, its various derivatives, and the common intravenous solutions. If this clinic has helped to clarify some of these principles and to indicate some of the therapeutic possibilities arising from the separation of blood into its component parts, it will have achieved its objective.

## BIBLIOGRAPHY

- 1 Cohn, E. J. Blood Proteins and Their Therapeutic Value. *Science*, 101: 51, 1945
- 2 Gamble, J. L. *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid*. A Lecture Syllabus. Cambridge, Harvard Press, 1942
- 3 Ashworth, C. T. and Adams, G. Relationship of Specific Gravity of Whole Blood to Specific Gravity of Plasma, Red Blood Cell Count, Hematocrit, and Hemoglobin as Indicators of Hemoconcentration. *J. Lab. & Clin. Med.*, 26: 1934, 1941
- 4 Phillips, R. A., Van Slyke, D. D., Dole, V. P., Emerson, K., Jr., Hamilton, P. B. and Archibald, R. M. Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma. Report from U. S. Naval Research Unit at the Hospital of the Rockefeller Institute for Medical Research, 1943
- 5 Harkins, H. N. The Treatment of Burns in Wartime. *J.A.M.A.*, 119: 385, 1942
- 6 Shen, S. C., Ham, T. H. and Fleming, E. M. Studies on Destruction of Red Blood Cells. III. Mechanism and Complications of Hemoglobinuria in Patients with Thermal Burns, Spherocytosis and Increased Osmotic Fragility of Red Blood Cells. *New England J. Med.*, 229: 701, 1943
- 7 Ross, J. F. Blood Banks and Blood Transfusion. *New England J. Med.*, 230: 171 and 195, 1944
- 8 Landsteiner, K. and Wiener, A. S. An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood. *Proc. Soc. Exper. Biol. & Med.*, 45: 223, 1940
- 9 Diamond, L. K. The Clinical Importance of the Rh Blood Type. *New England J. Med.*, 232: 447, 1945
- 10 Taylor, G. L. Tests for Rh Factor and Its Antibody. *Proc. Roy. Soc. Med.*, 36: 225, 1943

- 1 Wiener A. S. Hemolytic Transfusion Reactions. III Prevention, with Special Reference to Rh and Cross Match Tests. *Am. J. Clin. Path.*, 12 302, 1942
- 2 Loutit, J. F. and Mollison P. L. Advantages of Disodium Citrate-Glucose Mixture as Blood Preservative. *Brit. Med. J.*, 2 744, 1943
- 3 De Gowin, E. L. The Possible Role of Whole Blood Transfusions in Military Medicine. *J.A.M.A.*, 127 1037, 1945
- 4 Kleodshoj, N. C., McNeil C., Swanson, P. and Witebsky E. Transfusion of Conditioned Universal Blood. *Arch. Int. Med.*, 70 1 1942
- 5 Taylor E. S., Thalhimer W. and Cooksey W. B. The Organization of a Red Blood Cell Transfusion Service. *J.A.M.A.*, 124 958 1944
- 6 Cooksey W. B. and Horwitz, W. H. Use of Salvaged Red Cells. *Ibid.*, p 961
- 7 Pillemer L., Oncley J. L., Melin, M., Elliott, J. and Hutchinson, M. C. The Separation and Concentration of Isohemagglutinins from Group-Specific Human Plasma. *J. Clin. Investigation*, 23 550 1944
- 8 De Gowin E. L. Appraisal of Isohemagglutinin Activity *Ibid.*, p 554
- 9 Elliott, J., Busby G. F. and Tatum, W. L. Some Factors and Observations on Preparation and Preservation of Dilute Plasma. *J.A.M.A.*, 115 1006, 1940
- 10 Lozner E. L. and Newhouser, L. R. Preservation of Normal Human Plasma in the Liquid State. I. A Statistical Study of 1751 Administrations. *J. Clin. Investigation*, 23 343, 1944
- 11 Taylor F. H. L., Lozner E. L., Davidson, C. S., Tagnon, H. J. and Newhouser L. R. II. Comparative *in vitro* Studies on the Physiologic Activity of Labile Constituents of Liquid and Frozen Plasma *Ibid.*, p 351
- 12 Strumia, M. M. and McGraw, J. J. Blood Plasma and Its Place in the Practice of Medicine with Special Consideration to the Problems of Preservation. *J.A.M.A.*, 118 427, 1942.
- 13 Strumia, M. M. and McGraw J. J. Frozen and Dried Plasma for Civil and Military Use. *J.A.M.A.*, 116 2378, 1941.
- 14 Taylor, F. H. L., Levenson, S. M., Davidson C. S., Browder N. C. and Leach C. C. Problems of Protein Nutrition in Burned Patients. *Ann. Surg.* 118 215 1943
- 15 Cope, O., Nathanson, I. T., Rourke, C. M. and Wilson, H. Metabolic Observations (on Burns) *Ann. Surg.*, 117 937, 1943
- 16 Lyons, C. Problems of Infection and Chemotherapy (in Burns) *Ibid.*, p 94
- 17 (a) Harrell, G. T., Venning W. and Wolff W. A. The Treatment of Rocky Mountain Spotted Fever with Particular Reference to Intravenous Fluids. A New Approach to Basic Supportive Therapy. *J.A.M.A.*, 125 1944
- 18 (b) Weinberg L. D. and McGavack, T. H. The Wernicke-Korsakow Syndrome. *New England J. Med.*, 232 95 1945
- 19 Jaesway C. A. The Plasma Proteins, Their Importance in Clinical Medicine and Surgery. *New England J. Med.*, 229 751, 79 1943
- 20 Armstrong S. H., Jr., England, A. C., Jr., Favon, C. E. and Sherry, L. H. Anemia and Hypoproteinemia Complicating Penicillin Therapy with Penicillin. Role of Specific Supportive Therapy. *J.A.M.A.*, 127 303 1945
- 21 Shohl, A. T., Butler A. M., Blackfan, K. D. and Macdonald, E. Nitrogen Metabolism during the Oral and Parenteral Administration of the Amino Acids of Hydrolyzed Casein. *J. Pediatr.*, 1 400 1952
- 22 Post, J. and Patek, A. J., Jr. Serum Protein in Relation to Liver Disease. *Bull. New York Acad. Med.*, 152 1 1956



- 32 Elman, R., Brown, F A, Jr, and Wolf, H Studies on Hypoalbuminemia Produced by Protein Deficient Diets II Rapid Correction of Hypoalbuminemia with an *ad libitum* Meat Diet. J Exper Med., 75 461, 1942
- 33 (a) Taylor, F H L, Davidson, C S, Tagnon, H J, Adams, M A., MacDonald, A H and Minot, G R Studies in Blood Coagulation The Coagulation Properties of Certain Globulin Fractions of Normal Human Plasma *in vitro* J Clin Investigation (in press)
- (b) Minot, G R, Davidson, C S, Lewis, J H., Tagnon, H J and Taylor, F H L, Coagulation Defect in Hemophilia The Effect in Hemophilia of the Parenteral Administration of a Fraction of the Plasma Globulins Rich in Fibrinogen *Ibid*
- 34 Thalhimer, W The Value of Convalescent Scarlet Fever, Measles, and Mumps Serums in Prophylaxis and Therapy M CLIN NORTH AMERICA, 23 613, 1939
- 35 For references on the products of plasma fractionation, the reader is referred to
- (a) Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation J Clin Investigation, 23 417-606 (July) 1944 A series of twenty-three papers)
- (b) Clinical Use of Products of Human Plasma Fractionation I Janeway, C. A Albumin in Shock and Hypoproteinemia II Janeway, C. A Gamma Globulin in Measles III Ingraham, F D and Bailey, O T The Use of Products of Fibrinogen and Thrombin in Surgery J.A.M.A., 126 674, 1944
- 36 Scatchard, G Strong, L E. Hughes, W L, Jr, Ashworth, J N and Sparrow, A H Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation XXVI The Properties of Solutions of Human Serum Albumin of Low Salt Content J Clin Investigation (in press)
- 37 Thorn, G W, Armstrong, S H, Jr, Dickerson, V C, Woodruff, L M and Tyler, F H Chemical, Clinical and Immunological Studies on the Products of Human Plasma Fractionation XXVII Use of Salt-Poor Concentrated Human Serum Albumin Solution in the Treatment of Chronic Bright's Disease *Ibid*
- 38 Greenberg, M, Frant, S and Rutstein, D D "Gamma Globulin" and "Placental Globulin," a Comparison of Their Effectiveness in the Prevention and Modification of Measles J.A.M.A., 126 944, 1944
- 39 Stokes, J, Jr., and Neefe, J R. The Prevention and Attenuation of Infectious Hepatitis by Gamma Globulin J.A.M.A., 127 144, 1945
- 40 Neefe, J R, Miller, T G and Chornock, F W Homologous Serum Jaundice A Review of the Literature and Report of a Case Am J Med Sc, 207 626, 1944
- 41 Neefe, J R., Stokes, J, Jr, Reinhold, J G and Lukens, F D W Hepatitis Due to the Injection of Homologous Blood Products in Human Volunteers J Clin Investigation, 23 836, 1944

## TREATMENT OF COMMON DERMATOSES

JOHN G. DOWNING, M.D. \*

THE treatment of cutaneous disturbances is comparatively simple when the causative factor is identified and eliminated. The pruritus of the diabetic disappears with a proper dietary regimen, the inflammatory reactions of rhus poisoning quickly subside after the removal of oil from the skin and the application of suitable wet dressings, lotions and pastes.

Unfortunately the slightest eruption of the skin seems to call for immediate action, even though there may be no pain or itching. Advice is sought and freely given by the relative, neighbor or friend. The original eruption, a transient erythema or a cancer, is no longer recognizable when the patient reaches the dermatologist, due to overtreatment. A large percentage of a dermatologist's clientele is composed of patients suffering from irritations and hypersensitivities resulting from injudicious use of proprietary medicines, the prescribing of wrong medication as a result of mistaken diagnoses, and the prescribing of sensitizing drugs such as the sulfonamides, mercury, resorcin and the cocaine derivatives for topical application. These drugs are valuable when indicated, but their sensitizing faults should be explained to the patient who should test a small area of his skin before extensive application. Any extension of the eruption should be a warning for change of medication.

Routine history should record the previous treatment in sequence. Thorough examination and suitable laboratory procedure should establish a proper diagnosis. Dermatitis venenata from allergens ranks first, by far, in my office list of diagnoses, and in these cases only topical applications are needed.

Topical therapy is still in the realm of trial and error and, from observation of the formulas of some proprietary remedies, it would seem that we have not advanced far from the magic brews of the ancients. A complete knowledge of all dermatologic remedies is impossible and unnecessary. If restrictions became very extreme, I could still relieve a good percentage of my patients with salt vinegar, boric acid, corn starch, water and petrolatum.

As the result of advertising by radio, press and other methods America has become skin conscious. Some try to enhance the beauty of a normal skin, while others attempt to remove the blemishes. The

---

\* Professor of Dermatology and Syphilology, Tufts College Medical School; Professor of Dermatology, Boston University School of Medicine; Dermatologist in Chief at St. Elizabeth's Hospital, the Boston City Hospital and the Massachusetts Memorial Hospitals.

layman may be excused for heeding this propaganda, but not the physician. He has his medical education which should have taught him to consult recent approved textbooks—the United States Pharmacopoeia, the National Formulary, the publications of the American Medical Association and the American Pharmaceutical Association, and lastly the advice of the Council of Pharmacy and Chemistry in dermatology and syphilology, either directly or through its annual volume of New and Nonofficial Remedies. A sufficient knowledge of drugs advocated by experienced dermatologists is necessary, and their indications and contraindications, as well as the proper methods of application, should be known. Printed instructions are of great value, and the physician should know the necessary amount to be used and prescribe neither too much nor too little. An ounce of an ointment is sufficient for only one application to the average adult body.

**Psychic Factors**—Before prescribing any medication one must evaluate the psychic reaction of the patient to the rebellious outburst of the skin. There is nothing more disturbing to the average individual than an unexpected or recalcitrant disfigurement or disturbance of the skin. The diagnosis, the prognosis and the possible effects of medication must be explained to the patient. No disease should be pronounced incurable unless an unquestionable diagnosis is made of an entity which has been proved to resist all therapy. I have seen cases of psoriasis that did not recur for fifteen or more years. Cases misdiagnosed by more than one experienced observer as pemphigus have healed and remained well. There is a great psychic factor in the background of many cutaneous diseases. It alone may be the cause of pruritus, urticaria, angioneurotic edema, dermatitis factitia, phobias, hyperhidrosis, pompholyx, and changes or loss of hair. In my experience, psychic traumas have caused exacerbations of neurodermatitis, lichen planus and psoriasis. I have seen all three greatly improved by psychosomatic therapy, after proper dermatologic therapy alone had failed. A certain amount of psychotherapy is of value in all types of dermatologic patients. Even a man with a small benign basal cell epithelioma may develop a phobia unless he is assured that this lesion can be cured. Therefore, the first step in therapy should be reassurance, not a defeatist attitude of "try this and see what happens." A knowledge of drugs and their actions will give confidence to the physician which he in turn will impart to his patient. The following briefly summarizes these remedies.

#### TOPICAL APPLICATIONS

**Baths**—Baths have a definite value in cleansing and soothing the skin. Since soap is contraindicated, corn starch or a combination of oatmeal and sodium bicarbonate—the so-called *colloid bath*—should be used. The water should not be hot, rather about 98° F.

**Wet Dressings**—There is nothing more soothing to an acutely in-

flamed surface than wet dressings of solution of boric acid, 2 per cent, or aluminum acetate, 2 to 8 per cent. These should not be allowed to dry on the skin, and should not be used more than twenty-four to forty-eight hours, for they cause maceration.

**Powders**—Powders are valuable but neglected remedies. They are cooling and drying, and are an excellent method of applying drugs to the skin. The mineral substances are best—talc, zinc oxide, calcium carbonate, magnesium carbonate and kaolin. Because of caking and hardening—a cause of their unpopularity—they are not to be used on oozing surfaces except when alternated with warm, wet dressings. On the unbroken skin they are very soothing and are used frequently in erythrodermas. A reddened, healing area may be protected by a borated talc. All women know the value of face powder to enhance the beauty of the skin and to remove oiliness. The addition of sulfur may be of value in acne. Powders should be used on moist feet and are good prophylactics against some forms of fungous infections. The following is an example

Salicylic Acid	3.0
Zinc Oxide	6.0
Boric Acid, impalpable	12.0
Talc	q.s. ad 120.0

The present Army issue foot powder has the following composition<sup>1</sup>

Salicylic Acid	2.0
Boric Acid	6.0
Zinc Stearate	3.0
Exsiccated Alum	1.0
Starch	10.0
Talc	78.0

When the skin is exposed to constant wetting, as from urine or sweat in a bedridden patient, a fatty powder such as the following<sup>2</sup> may be used

Magnesium Stearate	12.0
Liquid Petrolatum	12.0
Talc	q.s. ad 120.0

Sulfur and DDT are used for parasiticides.

**Lotions**.—Lotions are the next step in therapy. They are suspensions of powders and are of value in the treatment of congested and oozing surfaces. The most popular lotion is Calamine Lotion, N.F. VII. This contains a colloidal clay called bentonite, which acts as a medium for suspending the powders in the liquid by producing a gel. A more elegant preparation is made by the addition of Neocalamine Lotion, N.F. VII, in sufficient amount to match the patient's skin, to avoid the "circus clown's" appearance. The addition of phenol, 1 to 2 per cent, and menthol 0.25 to 0.5 per cent, relieves the pruritus. To achieve a fine dispersion of the menthol, it should be dissolved in a small quan-

tity of alcohol before being incorporated into the lotion. The pharmacist realizes this necessity and may be depended upon to carry out the procedure without specific instructions to do so. Goodman<sup>3</sup> suggests a formula for suspension of colored zinc oxide (calamine or neocalamine)

Stearic Acid	40
Triethanolamine	10
Distilled water	q s ad 1000
To which add	
(a) Prepared Calamine	80
Zinc Oxide	80
or (b) Prepared Neocalamine	150
or (c) Prepared Neocalamine	80
Zinc Oxide	40

Many useful formulas, such as the following,<sup>4</sup> may be prepared using bentonite

Bismuth Subcarbonate	250
Bentonite, 6%, in Lime Water	ad 1200
Zinc Oxide	60
Talc	60
Sodium Borate	60
Menthol	09
Alcohol	180
Bentonite, 6%, in Lime Water	ad 1200

**Pastes**—When the acute inflammation has subsided, the use of an oily preparation or a paste is indicated. C. J. White taught that when the skin began to look like a peeling whitewashed fence, then it was time for oily or greasy vehicles. Their action is more prolonged and they adhere to and soften the scales and crusts. A paste is a rather stiff preparation consisting of powders and the vehicle which may be glycerin, hydrocarbons, paraffin, petrolatum, animal or vegetable fats, lard, cocoa butter, yellow wax, various expressed oils, or mixtures of these. Those containing glycerin are watery pastes. Two examples follow.

Starch	120
Distilled Water	240
Glycerin	q s ad 1200
Zinc Oxide,	
Talc,	
Glycerin,	
Distilled Water	aa 300

Those having a base of petrolatum, such as the official paste of zinc oxide, are the most popular. However, as too much zinc oxide is apt to cause a folliculitis on a hairy surface, I prefer the following<sup>5</sup>

Zinc Oxide	2.0
Starch	13 0
Petrolatum	15 0
Solution of Aluminum Acetate	10 0
Lanolin	20.0
Zinc Oxide Paste	30.0

Salicylic acid, sulfur and sulfonated bitumen may be added to pastes, when indicated

**Liniments or Emulsions**—Pastes are usually used after the application of a lotion. To avoid the writing of two prescriptions, I prescribe a mixture of the lotion and oil, as a liniment or an emulsion, of which Calamine Liniment, N.F. VII, and the cuticolored Neocalamine Liniment, N.F. VII, are excellent examples. When antipruritics are added to these, they must be greatly reduced in amount to avoid irritation, due to the prolonged action of the oil. Pusey's modification<sup>6</sup> is an excellent one, but an experienced pharmacist is required for its compounding

Tragacanth	4.00
Phenol	0.75
Zinc Oxide	30.00
Calamine	30.00
Olive Oil	120.00
Distilled Water	q.s. ad 500.00
Oil of Bergamot	1 to 2 cc.

Other drugs such as menthol, resorcin and camphor may be added to the above. In cases of marked pruritus, I frequently use the following

Solution of Coal Tar	15 0
Solution of Lead Subacetate	15 0
Olive Oil	80.0
Starch	30.0
Lime Water	q.s. ad 240 0

Mix the solution of lead subacetate with the olive oil and about 15 cc. of lime water. Add the rest of the lime water in very small portions, stirring thoroughly after each addition. When the emulsion has been completed the solution of coal tar and the starch are added.

Liniments used where there is not much oozing are ideal in erythematous squamous eruptions such as early psoriasis, lichen planus, pityriasis rosea, the various erythrodermas and the subacute stage of contact dermatitides. A favorite prescription of mine in the pruritic type of psoriasis is the following<sup>7</sup>

Solution of Coal Tar	12 0
Olive Oil,	
Bentonite, 6% in Lime Water	22 50.0
Lime Water	10 0

In prescribing liniments other than those of the National Formulary I generally write the directions for mixing and advise the use of an

electric mixer I usually prescribe the oil-in-water type of emulsion, because I want the medicament to reach the skin. This must be borne in mind when a water-soluble substance such as penicillin is incorporated in these vehicles.

In asymptomatic erythematous and papular eruptions, and macular, scaly eruptions such as pityriasis rosea, if there is no itching, there is no need of local applications. In pruritic eruptions, such as urticaria, there is no need for lotions containing insoluble substances. Simple watery or alcoholic solutions containing 0.5 to 1 per cent of menthol are more cooling and more antipruritic. *Astringent lotions*, such as the following,<sup>8</sup> are of value in acne.

Precipitated Sulfur	10 0
Spirit of Camphor	10 0
Alcohol	80 0
Solution of Methyl Cellulose, 2% (1500 cps)	30 0
Rose Water	qs ad 240 0

**Ointments, Creams and Oils.**—It is in the use of the final category of dermatologic preparations that complications arise, namely in the use of ointments. I advise the inexperienced student to use an ointment as his last choice. Having no evaporating properties, being comparatively free of water, they cause congestion and irritation. However, when properly used, they are of extreme value. Their sale is, perhaps, the most profitable business of modern times. They are promoted as milady's creams for beauty, the rejuvenators of the old, the rectifiers of nutritional deficiencies, and the cure for all ailments from pneumonia to psoriasis. I saw one that was recommended for cardiac disturbances. They are the subject of tremendous research, and their value for introducing medication by absorption was recognized by the ancients, but apparently forgotten by many modern physicians. One must be mindful of the purpose for which he prescribes an ointment, must realize the danger of the absorption of the drug incorporated, and watch for untoward reactions locally or systemically. Many ointments are messy, obnoxious preparations, stain everything they contact, are difficult to remove, and cause a great economic loss, for, while the patient is using them, he dislikes to mingle with his fellow-workers and stops work.

A glance through pharmaceutical journals will show the efforts of the pharmacist to remedy these faults, which already have been recognized by the makers of proprietary preparations, with consequent increased popularity of their products. Again, the recent use of endocrines and sulfonamides, and the future use of penicillin have stimulated research for the vehicles by which they may best reach and penetrate the skin, an impossibility with petrolatum and lanolin. Fantus<sup>9</sup> listed the following ointment vehicles: cerates, ointments, cream ointments (cold creams). The cerates, due to the presence of

wax, have a melting point above the temperature of the skin. Therefore, they do not liquefy, stay in the place where they are wanted, and keep the dressing from sticking to raw surfaces. They are useless for applying medication other than volatile substances. Ointments liquefy at body temperature and, to a certain extent, carry the medication to the skin. Cream ointments have water incorporated in them by means of emulsification and give a cooling sensation due to its evaporation, hence the name "cold cream." Their amazing and profitable acceptance as cosmetics has taught physicians and pharmacists to copy them. A favorite prescription of mine for a mild pruritic eruption contains cold cream.

Menthol	0.3
Phenol	0.9
Boric Acid Ointment	29.0
Rose Water Ointment	ad 60.0

Another excellent but somewhat complicated mixture is of the vanishing cream type.

Stearic Acid	10.0
Triethanolamine	1.0
Glycerin	15.0
Distilled Water	34.0
Alcohol	10.0
Rose Water	30.0
Phenol	1.0
Menthol	0.6
Wool Fat	4.0
White Petrolatum	14.0

Melt the stearic acid, wool fat and white petrolatum on a water bath and heat to 80° C. Mix the triethanolamine, glycerin, rose water and distilled water and heat to 80° C. Add the aqueous phase to the oil phase, stirring constantly and allow to cool to 50° C. Add the phenol and the menthol, previously dissolved in the alcohol, and stir until the product is homogeneous.

Salicylic acid in amounts larger than 2 per cent usually breaks down cold creams, but O'Brien found the following cold cream effective in a modification of Whitfield's Ointment.<sup>10</sup>

White Wax	13.0
Cerestin	6.4
Mineral Oil	55.0
Sodium Borate	0.6
Distilled Water	25.0

He suggests that, with this base the official strength of salicylic acid and benzoic acid be reduced one-half and that 2.5 per cent of thymol be added.

Benzoic Acid	6.0
Salicylic Acid	3.0
Thymol	2.5
Mineral Oil	2.5
Cold Cream	q.s. ad 100.0



The inclusion of small amounts of some of the newer emulsifying agents in ointment bases facilitates their removal from the body. This is exemplified in the formula which follows,<sup>11</sup> in which the base consists of diglycol stearate, 5 per cent, and petrolatum, 95 per cent

Crude Coal Tar	2 0
Zinc Oxide	2 0
Starch	15 0
Base	15 0

Many excellent washable bases have been recommended by Duemling.<sup>12</sup> In the use of tar, I have had excellent results with the following

Crude Coal Tar	2 0
Sodium Lauryl Sulfate	0 8
Cetyl Alcohol	15 0
Glycerin	5 0
White Petrolatum	14 0
Distilled Water	35 0

The base whose formula follows is an excellent vehicle for ammoniated mercury, phenol, tannic acid, zinc oxide and ichthammol but is not suitable for boric acid and salicylic acid

Glyceryl Monostearate	15 0
Cetyl Alcohol	15 0
Glycerin	35 0
Diethylene Glycol	35 0

A base which is compatible with all of the substances mentioned above has been recommended by Beeler.<sup>13</sup>

Cetyl Alcohol	15 0
White Wax	1 0
Propylene Glycol	10 0
Sodium Lauryl Sulfate	2 0
Distilled Water	72 0

Cetyl alcohol has the chemical formula  $\text{CH}_3-(\text{CH}_2)_{14}\text{CH}_2\text{OH}$ . It is manufactured by E. I. DuPont de Nemours, Inc. of Wilmington, Delaware, who also market sodium lauryl sulfate under the trade name of Duponol C. Cetyl alcohol is greaseless, a good emollient, and renders the skin velvety. Its penetrating power in combination with a wetting agent such as sodium lauryl sulfate causes medicaments to be readily transferred through the skin. The effectiveness of wetting agents is based on their power of reducing surface tension between solid and solvent, thus permitting rapid penetration and dispersion of the solid. Because of this property they are useful as detergents and penetrants, and some of these agents are also efficient emulsifiers. Propylene glycol ( $\text{CH}_3\text{CHOH}-\text{CH}_2\text{OH}$ ) imparts ease of spread and softness, and retards the evaporation of water. The above ointment base has been shown to be of the oil-in-water type. Its pH is reported to be within the range of 7 to 9, and is, therefore, well on the alkaline

side. No apparent incompatibilities have been found for this base as far as the experimental work has progressed

Pectin emulsion and ointments have been tried, but further research is necessary due to incompatibilities. A 15 per cent suspension of bentonite in water has been used as an ointment base on the body and scalp.<sup>14</sup>

Kulchar<sup>15</sup> recommends elkonite as a colloidal clay ointment base. Its advantage is that it is fairly adherent, but may be readily removed by gentle washing with water. It is used in a 15 per cent concentration as a gel.

Triethanolamine is an excellent emulsifying agent. I have used it in a cleansing cream for acne for many years.<sup>16</sup>

Benzyl benzoate has been found to be effective against pediculosis capitis, and has been used for seven years in the treatment of scabies. A concentrate is made with 2 gm. of triethanolamine, 8 gm. of oleic acid, and sufficient benzyl benzoate to make 100 cc.<sup>17</sup>

With the marked increase of industrial dermatitis, many efforts have been made to produce *protective creams* for the worker. The perfect protective cream has not been found, the failure being mainly due to the skin itself. Skins vary, some have an excess of oil, others have an excess of water; some are greasy, others are dry. The soap or the cream must, therefore, be selected for the individual, not for a group of workers. The choice depends usually on the amount of water or oil on the skin. The protective cream should be inexpensive, easily applied and removed, an elegant preparation, not too greasy or drying, and should contain no irritating or sensitizing ingredients. The following<sup>18</sup> is an example

Stearic Acid	10.0
White Wax	2.0
White Petrolatum	4.5
Triethanolamine	1.5
Glycerin	8.0
Distilled Water	54.0
Talc	20.0
Perfume	as desired

Tar is one of the most useful drugs in dermatology, but patients object to its uncleanness and its staining properties. Many efforts have been made to offset these objections. Tars differ greatly in their composition. An effort should be made to improve the inadequate specifications of the official product. Steam distillates of tar make pleasant preparations, but are not always effectual.

Snake venom has been used in an ointment for chilblains.

Concentrated sulfur pastes have been found by Abramowitz<sup>19</sup> to be of value in pustular psoriasis, infectious eczematoid dermatitis, and scabies. Incorporated with white or yellow petrolatum in a concentration of 30 per cent in cold, 40 per cent in water.

spread on thinly However, in acne rosacea, my favorite is the following

Salicylic Acid	20
Precipitated Sulfur	20
Petrolatum	qs ad 300

This formula is also of great value in impetigo contagiosa

Recently, extensive studies have been made in the use of the cutaneous route,<sup>21-24</sup> rather than injection, of drugs such as endocrines In prescribing ointments, we must always remember the effect desired for the drug incorporated, and watch for undesired effects

### INJECTIONS

In 1931 I reported the effect of calcium in pruritic skin affections, with special reference to calcium gluconate, a new compound in this country<sup>25</sup> Before this paper was published, a patient with pernicious vomiting, who had miscarried twice as a result of the affliction, was given calcium gluconate intravenously for a severe attack of urticaria, with successful elimination of the urticaria and the vomiting Thus a dermatologist may have been a pioneer in this field However, when I see patients today who have had injections of calcium gluconate day after day, week after week, with no results except the depletion of their pocketbooks, I wish I had never published that report. It is of value in a few acute conditions, but after a few injections calcium can be given by mouth with the same satisfactory result.

The same holds true for other forms of calcium Calcium chloride is very irritating and painful, if any of the solution extravasates into the tissue Calcibronat intravenously and orally gives temporary relief to tense sufferers of neurodermatitis, but it should not be used too long because of the danger of bromism Sodium iodide intravenously had a vogue in herpes zoster, I saw one good result in a case of herpes zoster ophthalmicus but in other cases this treatment appeared valueless

Several cases of carbuncles and furunculosis appeared to be benefited by the use of aolan, but it became unpopular in my practice after abscesses appeared at the sites of injection in two patients Collosal manganese seems to be of value in an occasional case of sycosis vulgaris, but useless in other diseases Sodium thiosulfate gives transient relief from itching in cases of dermatitis exfoliativa from drugs, but I do not believe it shortens the duration of the disease Although it has been claimed that the subcutaneous injection of sodium thiosulfate in situ is a means of preventing inflammation and pain after the accidental extravasation of the salvarsan, I prefer the injection of novocaine into these areas

Enesol, a proprietary compound containing both arsenic and mercury, is of value in the acute cases of lichen planus However, since it has not been available, I have used bismuth subsalicylate with almost

as good results Autogenous vaccine and toxoid should be tried in a stubborn case of acne or recurrent staphylococcal infection of the skin Gold sodium thiosulfate has been recommended for several cutaneous diseases, including psoriasis, but in my experience its chief value is in lupus erythematosus, in the chronic or late subacute stage. It is a dangerous drug I have seen two deaths and several cases of dermatitis exfoliativa following its use.

Parenteral administration of toxicodendrum as a prophylactic method in poison ivy dermatitis may have some value, but I am still unconvinced of its curative effect when used therapeutically I have used it since its introduction, and if the dermatitis showed signs of subsiding after the first injection, I gave another the following day, but no more. If the eruption was worse I did not give a second injection, for I have seen too many cases where I thought the eruption became generalized after these injections I thoroughly agree with the final statement of Stevens in his recent report on the status of poison ivy extracts "The treatment of the acute rash with ivy extracts should be discouraged, because many patients are made worse and there is no satisfactory evidence that any are helped" <sup>26</sup>

The value of the parenteral use of vitamins and endocrines is still in the experimental stage, but they do produce remarkable improvement when indicated. When one feels he must give an injection—either for the psychic effect or for want of something to do—the safest procedure is the injection of whole blood, autohemotherapy It is sometimes of value in extensive dermatitis venenata, urticaria and psoriasis. In these days of busy wartime practices and manpower shortage, it is remarkable how few injections are needed when proper internal medication, topical remedies and physiotherapy are used However one should be cognizant of the indications and contraindications, the dosage, and the method of administration. These may be learned from the reports of the National Research Council, such as the recent excellent report on penicillin by Dr Chester Keefer

#### HYPNOTICS

The choice of hypnotics in cutaneous disturbances is extremely important. In pruritic eruptions they will produce a short period of sleep, but the patient awakes with a terrific outburst of itching This fact is especially true when the barbiturates are used The depressing action of the hypnotic tends to increase the psychosis from which the patient is suffering Owing to their rapid action, paraldehyde and chloral hydrate are the drugs of choice. Chloral should be given in doses of 5 to 10 grains (0.3 to 0.6 gm.) Morphine lowers the threshold of the scratch reflex and should never be used Combinations of aspirin and codeine, although not good hypnotics, give a sense of relief and may be very useful In pruritic eruptions subsequent to phenobarbital therapy, it is well to remember to avoid phenol in local applications.

## THE SULFONAMIDES

The dermatologist, enthusiastic at first, early recognized the high incidence of sensitization from topical application of the sulfonamides, but despite his admonitions the general practitioner continued this use until he had a serious reaction in his own clientele. Although these calamities have become so numerous that now the lay public is cognizant and fearful, some pharmacists freely peddle sulfathiazole ointment over their counters and the two largest producers of band-aids continue to incorporate this dangerous drug in this universal first-aid application despite the fact that they are aware of the unfortunate results and of the resolution adopted by the Section of Dermatology and Syphilology of the American Medical Association.

The various sulfonamides are effective in the treatment of infections of the skin due to aerobic organisms such as streptococci and staphylococci. Sulfathiazole is more effective than sulfadiazine, sulfanilamide or sulfapyridine and is the drug of choice. The literature in 1941 advocated its use especially in impetigo. Later, sensitizations began to appear and it was recommended that it be used not over four days. The ointments containing as little as 5 per cent of sulfathiazole were found to cause the largest number of untoward results. Aqueous solutions, lotions and powders cause fewer accidents. However, approved textbooks do not recommend their use, because there are many harmless, time-honored remedies which are satisfactory for the relief of this minor disease.

I am thoroughly opposed to the topical application of these drugs, except in illnesses where withholding them might endanger life or lead to permanent disability, because I have seen too many cases of dermatitis exfoliativa of several months' duration in which the patient suffered untold torture unnecessarily. My worst cases have followed its use in varicose eczema.

All physicians are aware of the dangers of the oral use of the sulfonamide drugs, and as a result any untoward reaction is suspected by the patient owing to previous instruction by his physician, and subsequent confirmation leads to cessation of the drug. Most patients taking these drugs are hospitalized and under close observation, and the all too-frequent cutaneous reactions are readily recognized. With trepidation, I still use these drugs by the oral route in extensive pyogenic infections. I have used them in severe acne in large doses without success. Sulfapyridine, however, has a definite value in some cases of dermatitis herpetiformis. Physicians must remember the photosensitizing properties of the sulfonamides and not expose their patients to sunlight, ultraviolet or x-ray radiation while under treatment with them.

I have come to the conclusion that the dangers of the use of the sulfonamides in the practice of dermatology outweigh their benefits.

## ANTIBIOTICS

The phenomenon of antibiosis has been known to mycologists for nearly a century, but its practical application has been realized only recently. The first antibiotic to be successfully developed was *gramicidin*, a substance discovered in the cultures of *Bacillus brevis*. Its restriction to local use stimulated a search for a less toxic substance for internal medication, with the resulting development of penicillin. The substances derived from cultures of the *Bacillus brevis*, namely tyrothricin and gramicidin, are of value in discharging sinuses and pyogenic ulcerations. The substances derived from the higher fungi seem to be less toxic and more selective in their action. Although new agents already are appearing, streptothricin and streptomycin from the actinomycetes group, and patulin from the aspergillus group, penicillin is the one now best known.

## PENICILLIN

It has been my good fortune to be able to observe the results of the use of penicillin in the United States, especially in syphilitic infections, ever since the inauguration of the original work by the panel authorized by the Council of Pharmacy and Chemistry at the Evans Memorial Hospital, Boston. The results of the various cooperative groups are now well known through the many publications issued up to the present time.

In the beginning, only cases of syphilis showing a positive darkfield were submitted to penicillin therapy. The rapidity of the disappearance of spirochetes of the *Treponema pallidum* from the lesions in seven to twenty-four hours and their subsequent rapid healing was extraordinary. Herxheimer reactions were fairly common in the early stages but not serious, however, this fact must be kept in mind in treating cardiovascular, ophthalmic and aural disturbances. These reactions did not prevent the further administration of the penicillin.

The doses at first varied until a course of sixty injections, of 20,000 units each, given intramuscularly at three-hour intervals for seven and a half days was accepted as the minimum dosage schedule in primary and secondary syphilis. Later, however, military authorities insisted on larger doses of 40,000 units for the same period until 2,400,000 units were injected.

There were a few reactions of hypersensitivity, the most common being urticaria. This developed in almost 5 per cent of the patients with occasional joint pains. A vesicular eruption has been reported,<sup>27</sup> and I saw a bullous eruption appear in a patient treated for osteomyelitis.<sup>28</sup> There was surprisingly little pain at the site of injection, except in cases where the drug was accidentally injected subcutaneously. However when employing the intravenous route, pain and thrombosis frequently occurred at the site of injection.

Later at the Boston City Hospital and other clinics I observed its

use in congenital syphilis, and late cutaneous and osseous syphilis, with excellent clinical results. Although in my opinion late cutaneous lesions do not respond as rapidly as they did to the old arsphenamine and potassium iodide, still response is fairly prompt. It must be remembered that the use of penicillin is still in the stage of investigation, and positive assertions regarding cures cannot be made until at least a five- or ten-year period has elapsed. Perhaps later the administration of penicillin with an arsphenamine or heavy metal may be the method of choice. However, any drug properly administered at the right time that will give 80 per cent apparent cures must be considered remarkable.

As penicillin became more available, it was used in various cutaneous disturbances, especially those of staphylococcal or streptococcal infection, with varying success. Three cases of severe disseminated lupus erythematosus, two of pemphigus and one of erythema induratum failed to respond to penicillin. One case of hydradenitis responded promptly to 600,000 units, but recurred in a short time. Several cases of extensive cystic acne vulgaris involving the face and entire back had marked temporary improvement, but with the cessation of the injections new lesions immediately appeared, necessitating the regimen previously used in the treatment of the disease. The same was true of syccosis vulgaris. In these cases as high as 2,000,000 units were used with improvement, the eruption recurred after cessation of treatment.

Various types of local applications were used and finally a water-in-oil emulsion was prepared that was found satisfactory. While this preparation has not cured the disease it has markedly reduced the number of lesions, to the satisfaction of the patient. It has been found of value in impetigo contagiosa, provided that the usual cleansing methods are employed, namely washing the face with soap and water and removing the crusts.

One case of pemphigus neonatorum was successfully cured. Two days after birth the patient showed a bullous eruption which rapidly involved nearly all the cutaneous surface. Various sulfa drugs were used internally and externally with no improvement—the eruption continued to spread. On the eighth day I saw the patient and prescribed penicillin. Nineteen injections were given in two and a half days—eight doses of 5000 units and eleven doses of 2500 units—as well as local application of compresses of saline containing 500 units of penicillin per cubic centimeter. The response was almost immediate—within twenty-four hours the patient's temperature dropped, no new lesions appeared, and the old ones rapidly desquamated. In three days the skin was entirely healed except for two extremely adherent crusts, one on the left cheek and one on the right side of the neck. It was interesting to note that a small extremely adherent crust on the side of the neck was frequently daubed with a compress containing saline and penicillin. On the sixth day a reaction of irritation or hypersen-

sitization was noted around this lesion and spreading down onto the neck where the penicillin solution had dripped. This promptly healed without medication after the penicillin was stopped.

One case of chronic furunculosis was relieved as to the lesions present at the time of the injections, but new lesions appeared a few days after the last injection. Several cases of fungous infection of the skin were treated with penicillin ointment and emulsion, with satisfactory healing and disappearance of the pyogenic infection, but the intra-epithelial vesicles of dermatophytosis persisted after the cessation of treatment and required the use of fungicides. Two severe cases of impetiginous eczema of the lower legs, one in a twelve-year-old boy, were treated with 500,000 units every three hours with prompt improvement. However, when the pyogenic infection was cleared, there still remained the eczema to be treated with suitable therapy.

I believe penicillin will be a disappointment in general dermatologic therapy, not because the drug has not proved its worth, but because too much will be expected of it. Even when contraindicated, it will be tried with great expense and disappointment to the patient.

#### VITAMINS

Although man since his origin has had to maintain life by adequate intake of food, it is strange that accurate knowledge of nutrition is so meager. The study of vitamins has stimulated research in the field of nutrition to the advantage of dermatology. There is much to be known about these heretofore unknown substances so essential to normal growth and metabolism, and existing in minute quantities in our daily diet.

Deficiency of vitamins manifests itself frequently in cutaneous disturbances. At first it was thought that a given syndrome might be traceable to inadequate intake or storage of a single vitamin, but now it is recognized that it is due to multiple vitamin deficiency, though perhaps the loss of one may initiate the onset. Dietary fads, poverty, pestilence and war are frequently attended by stigmas of avitaminosis. The diet may be adequate, but failure to absorb the vitamin properly may result from chronic diarrhea, steatorrhea, pernicious anemia, disturbances of the endocrines and fevers due to infections.<sup>20</sup> Jeghers<sup>20</sup> in an excellent review describes numerous cutaneous changes of nutritional origin. He states that, in spite of the widespread use of vitamin preparations during the past ten years, the scarcity of untoward effects of excess vitamin ingestion indicates that these occur infrequently—and in general this is true. There are, however, two significant exceptions. Hypervitaminosis D is one of these. This is a condition characterized by hypercalcemia with resultant deposition of calcium in various tissues, which at times leads to a fatal termination. Such were the dangers of the use of massive doses of vitamin D in psoriasis a treatment which is now discarded by experienced dermatologists. He



also cited carotinemia, which may result either from ingestion of only moderate excess of carotene, or from impaired ability of the body to metabolize the amount of carotene present in a normal diet. I have seen cases of generalized pruritus which were relieved when the patient stopped taking large doses of vitamin B.

*Vitamin A* should be tried in follicular hyperkeratosis, keratosis pilaris, pityriasis rubra pilaris, keratosis follicularis, and loss of skin tissue as from burns and ulcers. It should be given in daily doses of 200,000 units.

*Vitamin B complex* has been used in many cutaneous diseases with varying success. Favorable results in acrodynia by the injection of 6 mg daily for six days were attributed to thiamine. Occasionally it seems to lessen the pain of postzoster neuritis,<sup>31</sup> though this relief may be somewhat psychic. Riboflavin has established its place in the treatment of the syndrome of cheilitis, perlèche, the brilliant-red, smooth tongue, and the scaling and keratotic plugging of the seborrheic area of the face, when given in doses of 20 mg daily. If given with accompanying doses of dilute hydrochloric acid, it is useful in the cutaneous eruptions and keratitis of acne rosacea. Recently I have been giving large doses in the treatment of the discoid type of lupus erythematosus with some success. Nicotinic acid has been a lifesaver in pellagra. It seems to be of value in the acute pyogenic infection. Pyridoxine has been recently reported as being of value in acne.<sup>32</sup> Liver extract parenterally or orally combined with iron certainly helps the adolescent chlorotic miss with acne.

Crandon and his associates<sup>33</sup> proved the need of *vitamin C* in certain types of hyperkeratotic lesions, petechial hemorrhages, and failure of wound healing. Sulzberger found that large amounts of vitamin C will raise the sensitivity threshold and that there will consequently be less danger of reaction to the use of the arsphenamines in syphilis. Cornbleet<sup>34</sup> showed its value in the removal of melanin deposition of Addison's disease.

Despite the many reports of the value of *vitamin D* in psoriasis, acne vulgaris, pemphigus and scleroderma, in my hands it has been a failure. It stimulates healing in x-ray burns.

*Vitamin P* is recommended in purpuras and for regulating vascular permeability, but not sufficient work has been done to prove this contention.

Vitamins to be of value must be used in adequate dosage and though they apparently are harmless, we still have a great deal to learn about them. They are expensive. The lay public is thoroughly victimized and vitaminized by advertising propaganda, and it is the physician's place to stem this tide, unless a definite deficiency in the patient is recognized.

## ENDOCRINES

Recent advances in endocrinology when applied to dermatology have initiated new concepts of therapy. The influence of the endocrine glands on the skin and its appendages is well known. Endocrine dysfunction has been frequently recognized by the cutaneous stigmata—loss of hair accompanied by a dry, scaly, infiltrated skin suggests hypothyroidism, the yellow, bronze or amber color of the skin must lead to the discovery of a dysfunction of the adrenal glands, the polychromatic patch on the lower leg may prompt the diagnosis of diabetes. These monoglandular aberrations may respond dramatically to hormonal therapy. However, the endocrine system is complex. No gland functions independently, they are closely interrelated, and a dysfunction of one overthrows the normal hormonal equilibrium so that response from one endocrine preparation is often disappointing.

The cutaneous changes at the menopause, namely the keratotic palms and soles, generalized pruritus and kraurosis, may respond dramatically to estrogens, but often they do not. Similarly in the male, the dry, scaly keratotic, pruritic skin may occasionally respond to androgens.

Acne vulgaris appears at puberty and therefore suggests a possible endocrine dysfunction. However, few youths escape the blemishes of this happy age, and it appears strange that nature should institute pathologic endocrine function at this period of life. Affecting so many it is a fertile and profitable field for endocrine experimentation, and in my opinion dangerous for uncontrolled unscientific therapy. The field of endocrine therapy in cutaneous diseases has tremendous possibilities, the response to fortunate selection of a hormone, and the giving of dosage previously determined by experimentation is often dramatic, as in the remarkable recovery after the use of 300 mg of testosterone propionate, when sulfa drugs, penicillin and vitamins had failed in a young girl prostrated by a disseminated lupus erythematosus showing the complete picture described by Libman and Sachs. Only in carefully studied cases of acne vulgaris, however, as in all cutaneous diseases, should hormones be used, for they are potent substances, and their indiscriminate use may lead to disastrous results.

## PHYSICAL THERAPY

Light, x-ray and radium play an important role in dermatologic therapy. Unsightly pigmentation may follow their use in acute eruptions, and all physicians are cognizant of the severe injury to healthy tissue which results from their misuse.

The air-cooled lamp is useful in acne, erysipelas, mycotic and pyogenic infections, pityriasis rosea and various forms of alopecia. The water-cooled mercury lamp is used in pitted scars resulting from acne, furuncles, carbuncles, ulcers, localized patches of psoriasis, tuberculosis of the skin and nevus flammeus.

The combination of crude coal tar and ultraviolet ray in the treatment of psoriasis has been used in Boston for many years with great temporary success. The tar is rubbed into the skin before ultraviolet radiation. Goeckerman,<sup>85</sup> however, perfected this treatment and first reported its success with patients at the Mayo Clinic.

### CONCLUSION

This article may seem to be one of destructive rather than constructive criticism. However, it is the result of many observations made in private practice. It is an attempt to add emphasis to the fact that many cutaneous diseases are self-limited, and are best treated conservatively with well-established beneficial methods of therapy. It is not an attempt to condemn experimental research for new advances, but to advise the physician to wait for results obtained by scientific experimentation developed by recognized clinics especially equipped for this type of work.

### BIBLIOGRAPHY

- 1 Pillsbury, D. M., Sulzberger, M. B. and Livingood, C. S. *Manual of Dermatology*, Philadelphia, W. B. Saunders Co., 1942.
- 2 *Pharmaceutical Recipe Book*, III.
- 3 Goodman, H. Calamine and Neocalamine. *Arch. Dermat. & Syph.*, 48(4) 369 (Oct.) 1943.
- 4 Hubbard, D. G. and Freeman, L. J. Further Uses of Bentonite. *J. Am. Pharm. A.*, Vol. 2, No. 2, Feb., 1941.
- 5 Abramowitz, E. W. Local Medication in Diseases of the Skin. *Arch. Dermat. & Syph.*, 23 644-680 (April) 1932.
- 6 Pusey, W. A. Calamine Liniment. *J. Cutan. Dis.*, 34 826, 1916.
- 7 *J. Am. Pharm. A.*, 2(2) 78 (Feb.) 1941.
- 8 Downing, Ohmart and Stoklosa. Sulfur in Dermatologic Preparations. *Arch. Dermat. & Syph.*, 50 8-9 (July) 1944.
- 9 Fantus, B. The Choice of Ointment Vehicles in Dermatology. *J. A. M. A.*, 107 861 (Sept. 12) 1936.
- 10 O'Brien, F. J. A New Modified Whitfield's Ointment. *J. Am. Pharm. A.*, Sept., 1941, pp. 376-378.
- 11 Downing, Ohmart and DiCicco. Coal Tar in Dermatologic Preparations. *Arch. Dermat. & Syph.*, 29 421-422 (June) 1944.
- 12 Duemling, W. W. *Arch. Dermat. & Syph.*, 43 264-280 (Feb.) 1941.
- 13 Beeler. *J. Am. Pharm. A.*, 3(7) 231 (July) 1942.
- 14 *J. Am. Pharm. A.*, Nov., 1941.
- 15 Kulchar, G. V. Elkonite, a Colloidal Clay Ointment Base. *Arch. Dermat. & Syph.*, 44 43 (July) 1941.
- 16 Downing, J. G. A New Cleansing Cream. *Arch. Dermat. & Syph.*, 30 243 (Aug.) 1934.
- 17 *J. Am. Pharm. A.*, March, 1945.
- 18 Downing, Ohmart and Stoklosa. A New Protective Cream. *Arch. Dermat. & Syph.*, 49 436 (June) 1944.
- 19 Watson, G. I. *Lancet*, March 1, 1941.
- 20 Abramowitz, E. W. *New York State J. Med.*, 43(8) 746-753 (April 15) 1943.
- 21 Walzer, A. and Sack, S. S. Cutaneous Absorption II. The Value of Petrolatum, Anhydrous Wool Fat and Other Bases in Percutaneous Absorption of Topically Applied Cottonseed Allergen. *Arch. Dermat. & Syph.*, 49 427 (July) 1944.

22. Wild, R. B. and Roberts, I. Absorption of Mercurials from Ointments Applied to the Skin. *Brit. M. J.*, 1 1076, 1926.
23. Macht, D. L. The Absorption of Drugs and Poisons through the Skin and Mucous Membranes. *J.A.M.A.*, 110-409 (Feb 5) 1938
24. McKee, G. M., Sulzberger, M. B., Herrman, F. and Bask, R. L. Histologic Studies on Percutaneous Penetration with Special Reference to the Effect of Vehicles. *J. Investigative Dermat.*, 6(1) 43 (Feb) 1945
25. Downing J. G. and Blumenfeld, A. The Effect of Calcium in Pruritic Skin Affections, with Especial Reference to Calcium Gluconate. *New England J. Med.*, 204 230 (Feb 5) 1931
26. Stevens, F. A. Status of Poison Ivy Extracts. *J.A.M.A.*, 127-912 (April 7) 1945
27. Anderson, D. G. The Treatment of Infections with Penicillin (Concluded). *New England J. Med.*, 232-423 (April 12) 1945
28. Morris, G. E. and Downing J. G. Bullous Dermatitis (Dermatitis Medicamentosa) from Penicillin. *J.A.M.A.*, 127 711 (March 24) 1945
29. Ebert, M. H.. Vitamins in Dermatology *M. CLIN. NORTH AMERICA*, 26(1) 47 (Jan) 1942.
30. Jeghers, H.. Skin Changes of Nutritional Origin. *New England J. Med.*, 228 (21) May 27, 1943
31. Goodman, M. J. *Calif. & West. Med.*, 51 1105-1106 (Aug) 1939
32. Jolliffe, N., Rosenblum, L. A. and Sawhully J. L. Effects of Pyridoxine on Persistent Adolescent Acne. *J. Investigative Dermat.*, 5 143 (June) 1942.
33. Crandon, J. H., Lund, L. C. and Dill, D. B. Experimental Human Scurvy. *New England J. Med.*, 223 353-369 1940
34. Cornbleet, T. Vitamin C and Pigment. *Arch. Dermat. & Syph.*, 35-471-479 1937
35. Goeckerman. *Canad. M. A. J.*, 48 34-36 (Jan.) 1943

## SUPPLEMENTARY REFERENCES

- Cornbleet, Theodore, Ingraham R. C. and Schorr Henry C.. Calcium Potassium and Sodium Metabolism and the Skin The Use of Potassium Chloride in Certain Allergic Dermatoses. *Arch. Dermat. & Syph.*, 46-833 (Dec.) 1942
- Duermillog Werner W. Weting Agents New Synthetic Chemicals of Use in Finer and More Efficient Topical Dermatologic Therapy. *Arch. Dermat. & Syph.*, 43 264 (Feb) 1941
- Isaak, Ludwig Treatment of Cutaneous Diseases with Radon Ointment and Radium Pads. A Preliminary Report. *Arch. Dermat. & Syph.*, 45-560 (March) 1947
- O'Leary Paul A. Vitamin Therapy in Dermatology and Syphilology. *Arch. Dermat. & Syph.*, 46-628 (Nov) 1942.
- Pillsbury Donald M., Livingood, Clarence S. and Nichols, Anna C. Bacterial Flora of the Normal Skin (Report of the Effect of Various Ointments and Solutions, with Comments on the Clinical Significance of This Study) *Arch. Dermat. & Syph.*, 45-61 (Jan.) 1942
- Strakosch, E. A. Studies on Ointments II. Ointments Containing Salicylic Acid. *Arch. Dermat. & Syph.*, 47 16 (Jan.) 1943
- Strakosch, E. A.. Studies in Ointments III Ointments Containing Sulfur. *Arch. Dermat. & Syph.*, 47 216 (Feb) 1943
- Strakosch E. A. Studies in Ointments VI Ointments Containing Chrysarobin. *Arch. Dermat. & Syph.*, 49 1 (Jan.) 1944
- Wallace, G. I., Day J. K. and Moorman, H. E. Chlorophyll Ointment in the Treatment of Dermatophytosis of the Feet and Similar Lesions. *Arch. Dermat. & Syph.*, 49 128-131 (Feb) 1944

## THE TREATMENT OF EPILEPSY

WILLIAM G. LENNOX, M.D.\*

IN the treatment of every disease, increased knowledge about that disease brings new opportunities and added responsibilities for the physician. Chemotherapy, for example, means added years of life for the patient, but also increased reading and study for the doctor. Tragic is the fate of the patient whose doctor has not been able to "keep up" with newly gained knowledge.

In recent years the gains against epilepsy have been as real, in relation to former knowledge, as those against infectious diseases, yet most patients, after visits to many doctors, are bewildered, discouraged, and still convulsing. This need not be. Epilepsy can no longer be classed as a "cause unknown" disease. The physician has at hand therapeutic weapons, both medicinal and social, which were lacking a dozen years ago. By means of the electroencephalograph, he can now look behind the patient's variegated and unpredictable seizures to the disordered electrical pulsations of his brain and thus gain a better insight into the type and extent of the disorder, and more intelligently select the drug most likely to succeed. The half million epileptics in the United States cannot be treated by a few specialists. The average epileptic must look to his own doctor, hoping that this doctor has sufficient interest in him and his problems and sufficient medical knowledge to give him treatment which is not traditional but modern.

Treatment of seizures cannot be instituted until two questions have been considered. First, is this person really epileptic? Second, what conditions in this particular patient are responsible for his seizures?

### IS THIS EPILEPSY?

The diagnosis of epilepsy seems disarmingly easy because the word describes a symptom or group of symptoms. Epilepsy is the Greek word for "seizure" so that any one who comes to his physician with the story of repeated sudden loss of consciousness, possibly with accompanying involuntary muscle movements or peculiar actions, is by definition an epileptic. However, by common consent various seizure phenomena have been set aside as nonepileptic. These include syncope, episodes which resemble syncope but are due to an irritable carotid sinus, periods of unconsciousness or amnesia due to hysteria, convulsions which occur in the course of toxemia of pregnancy, or uremia, or which are directly due to hypoglycemia, or to the ingestion

---

From the Department of Diseases of the Nervous System, Harvard Medical School, and the Children's Hospital of Boston.

\* Assistant Professor of Neurology, Harvard Medical School, Visiting Neurologist, Boston City Hospital, Visiting Physician, Children's Hospital of Boston.

of a convulsant drug Isolated convulsions which occur with fever in childhood are not epilepsy, although they have something like a 10 or 20 per cent chance of becoming so Excluded also are certain conditions which have some superficial resemblance to convulsive episodes but do not possess the cardinal feature of lost consciousness Examples are tetany or spasmophilia, chorea, sudden muscular collapse (cataplexy) which occurs in patients subject to narcolepsy, or inability to move on entering or leaving sleep (sleep paralysis) Strictly defined, localized convulsive movements without loss of consciousness, jacksonian epilepsy, should be excluded.

The diagnosis of epilepsy is made chiefly by exclusion (eliminating each of the above mentioned possibilities through careful history taking and appropriate examinations) In addition, positive evidence may be supplied by the electroencephalograph, when this is available.

In excluding conditions which resemble epilepsy, description of the seizure and of the surrounding events is of prime importance. Syncope almost always occurs when the person is upright, is preceded by symptoms of sympathetic perturbations, is attended by pallor and muscle flaccidity (except for a few clonic jerks) and is not followed by after-symptoms. The carotid sinus syncope is ruled out by failure to produce the syndrome by pressing on the sinus Hysteria is set in an emotional frame, the convulsive movements are bizarre and consciousness is not entirely absent. However, hysterical convulsions or periods of amnesia and psychomotor epilepsy are easily confused Convulsions due to hypoglycemia should occur long after a meal and be preceded by symptoms of hunger, weakness, sweating and fast pulse.

Physical or laboratory examinations may demonstrate disorders of circulation which lead to cerebral anemia, disease of the kidneys with resulting toxemia or disorders of metabolism like hypoglycemia or hypocalcemia. By far the most important laboratory test in differentiating epilepsy from other conditions is the electroencephalogram.

The Epileptic Fit—In diagnosing epilepsy by the description of the seizure, the physician must remember that there is no "typical" fit. Individual seizures are almost infinitely varied Nevertheless certain separations are possible Clinical descriptions or electroencephalographic (E.E.G.) tracings made during seizures permit segregation of epileptic seizures into seven types as in the accompanying table and Figure 162

#### SEVEN TYPES OF SEIZURES

1 *Jacksonian Epilepsy* Convulsive movements, or sensations, which begin in an extremity and spread upward in a "march" while consciousness is retained The seizures may end here, or continue into a grand mal, with loss of consciousness. Electroencephalogram High voltage fast waves begin locally and spread.

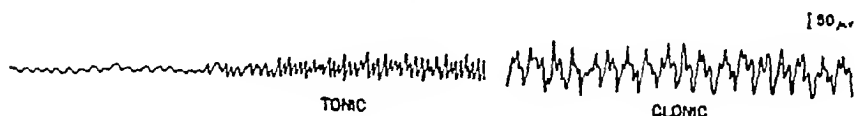
2. *Focal Fit* A grand mal convulsion which is predominantly or wholly one sided, or with initial turning of the head and eyes to one side, or has a localizing aura such as a peculiar odor Electroencephalogram During a convulsion as in grand mal in free period possibly a focus of very slow waves in area of a lesion, if this is in or near the cortex.

3 *Grand Mal* A convulsion, tonic and then clonic, involving the whole body, with unconsciousness Electroencephalogram Generalized high voltage fast waves

4 *Psychomotor, or Psychic Equivalent Seizure* A period of amnesia with or without tonic spasm or contortion of trunk muscles The person may appear to

### GRAND MAL SEIZURE

HIGH VOLTAGE FAST WAVES



### PETIT MAL SEIZURE

FAST WAVE AND SPIKE



### PETIT MAL VARIANT

SLOW WAVE AND SPIKE



### PSYCHOMOTOR ATTACK

HIGH VOLTAGE SQUARE AND SIX PER SEC WAVES

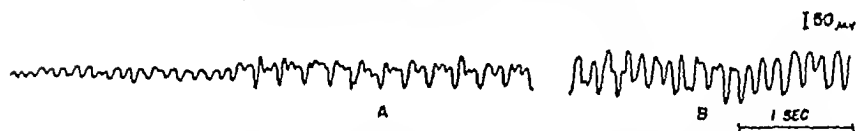


Fig 162 —The four different patterns of waves observed during four different types of seizures, grand mal (including jacksonian and focal), petit mal (also called pykno-epilepsy), petit mal variant (in which the association of seizure discharges and clinical symptoms may be vague or absent) and psychomotor In each case the left hand portion of the tracing is the person's normal record *A* and *B* in the bottom tracing represent different stages in this particular patient's seizure The horizontal line at the bottom indicates one second, and the perpendicular lines at the right the signal made by 50 or 200 microvolts of current. (Gibbs, F A., Gibbs, E. L and Lennox, W G Arch Neurol & Psychiat. 41 1111 [June] 1939)

act in a normal manner, or be confused or mutter, make chewing motions, have a "running fit," or become immobile with slow rotation of the body Manifestations are of extreme variety, often leading to the mistaken diagnosis of hysteria The patient has no memory of events during the attack and may be unaware that the attack has occurred





suggesting congenital maldevelopment of the brain, a story of birth injury, of cerebral or meningeal infections, or of certain cerebral diseases of later life, such as trauma, syphilis, tumors, or cerebral circulatory disorders. Second, a description of jacksonian seizures or of aura or convulsive movements confined to one side of the body. Third, neurological signs indicative of cerebral pathology. Fourth, laboratory evidence of cerebral pathology derived from roentgen rays of the skull or of the ventricular system (pneumoencephalogram) or from the electroencephalogram. In appraising the etiologic importance of brain pathology, the damage must have antedated the epilepsy, and not be merely the result of subsequent falls or convulsions.

**The Electroencephalogram**—Much the most important tool for determining the diagnosis, and the causes of seizures, and in guiding treatment is the electroencephalograph. Unfortunately this technic will only slowly become generally available. The apparatus is expensive and some widely advertised types are wholly unreliable. The making of satisfactory records and their proper interpretation requires even more experience and skill than the electrocardiograph. Artifacts may be confusing, the frequency and voltage of waves are modified by activity of brain or body or by sharp alterations in body chemistry, hence records must be made under standard conditions. However, the cost and trouble involved in obtaining dependable brain wave tracings is as nothing compared with the cost of epilepsy and the difficulties of treating it without the aid of this technic.

As with most other laboratory devices the electroencephalogram supplements but does not supplant diagnoses made from the description of seizures. The significance of a record varies with the degree of its abnormality. In a group of 1260 patients diagnosed as epileptic on clinical grounds, in 13 per cent the electroencephalogram was considered normal, in 29 per cent the waves were only moderately slow or fast, and hence weakly support a diagnosis made on clinical grounds, in 20 per cent waves were very slow or fast, and hence suggestive of epilepsy. In 38 per cent there were paroxysmal discharges of high voltage fast or slow waves, which are strongly suggestive of epilepsy. Half of these records with seizure discharges (19 per cent of all patients) were of the alternating dart and dome formation, which is diagnostic of petit mal.

The relative significance of various patterns is shown by their distribution in 730 adult epileptics, and in 1260 "normal" persons. Thirty-three of the epileptics had tracings with bursts of high voltage waves (seizure discharges) for each nonepileptic with this sort of tracing. The corresponding ratio for tracings with very slow or very fast waves of usual voltage was 20 to one, and for tracings with mildly slow or fast waves the ratio was two to one. For normal tracings the ratio was one in the epileptic group to six in the normal group.<sup>1</sup> In addition to giving substantial confirmation of the diagnosis in one-half

or more of cases, the electroencephalogram usually furnishes a clue as to the severity of the condition, a relatively normal record presumably carrying a good prognosis. The examination may also point to a localized cortical lesion, and may indicate the success of therapy, for the goal of treatment is to cure not only the seizures but also the associated cortical dysrhythmia. Finally, as a hereditary trait, recordings of the brain waves may help in tracing the heredity of epilepsy and in advising about marriage and children.<sup>2 3</sup>

#### FOUR FRONTS OF FREEDOM

Epilepsy needs to be attacked from all possible directions. Four of these have well defined possibilities: general hygiene and diet; neurosurgery, drug therapy, and social-psychological therapy.

**General Hygiene and Diet**—Maintenance of a good physique, avoidance of physical exhaustion and regularity of living are desirable goals. Aside from the correction of any specific abnormalities of function discovered in the physical examination, only common-sense rules need to be adopted. These refer to good posture, normal functioning of the digestive tract, regularity in habits of eating and sleeping, attention to proper exercise and recreation, and maintenance of a vigorous musculature. These are small items, but in the total reckoning are not above the attention of even the busiest of doctors. The diet should be adequate, but need not be specified unless constipation or other disturbance of function is present. In children a high fat, low carbohydrate (ketogenic) diet has often proved useful, especially for the control of petit mal. Wartime rationing increases the usual difficulties encountered in administering this diet. Limitation of fluids (the dehydration treatment) has also been advocated, but is also difficult of execution and in effectiveness falls far behind the use of drugs.

**Surgical Treatment**.—Only rarely is the evidence from a history of injury, of focal convulsions, or from pneumo- or electroencephalograph sufficiently strong to justify exploratory operation on the brain. Jacksonian seizures are more likely to call for operation than focal seizures. The most hopeful cases are slow-growing or cystic tumors, or scars involving the cortex, which are associated with localized rather than generalized cortical dysrhythmia. The chances of successful removal of a lesion and the nearby nerve cells which form a focus of abnormal discharge must be weighed against the danger of the procedure and the chances of a residual paralysis. Patient location of the trigger point by electrical exploration of the cortex and clean dissection is essential for success.

Whether exploration is urgent or not depends on the suspected pathology. Delay in removing a tumor may imperil life. Scar tissue, the result of severe trauma or penetrating gunshot wound, should be excised early for according to Penfield, the area of gliosis at the periphery of a cicatricial area tends to extend for years. Simple separation

of adhesions between the brain and meninges, or tying redundant blood vessels is of little or no avail. With careful selection of cases and expert surgical technic (plus postoperative use of drug therapy) the removal of cortical scars or superficial tumors may result in virtual freedom from seizures for as many as two-thirds of the patients. Any one contemplating neurosurgical attack on epilepsy should study the book by Penfield and Erickson.<sup>4</sup>

**Drug Therapy.**—The chief hope of controlling seizures lies in improving the chemistry of abnormally discharging nerve cells, through the administration of medicine. The physician now has a number of drugs from which to choose. Good results from treatment depend on discrimination in the choice of these and skill in determining the dosage best suited to the individual patient. No medicine should be continued unless adequate trial demonstrates that seizures are fewer or less severe with than without it. "Adequate trial" means daily use over months of time of each of the most effective drugs, each given in increasing amounts until either toxic symptoms appear—or seizures disappear. After two or three years of freedom (and an improved electroencephalogram) medicine may be stopped.

First we shall describe the various drugs and later discuss their choice.

*Bromides*, a phenomenal discovery when first used in 1857, are gradually assuming a place of historical importance only. For most patients they are the least effective of the anticonvulsants and, when given in considerable amounts, may cause unpleasant acneform eruptions and impair mental alertness. In order to maintain a certain level of bromide in the body, the chloride intake needs to be kept constant. A usual dose is 10 to 20 grains (0.6 to 1.2 gm) of sodium or potassium bromide given three times a day in a watery solution.

*Phenobarbital* has been in use since 1912. It is also sold under the trade name of luminal at a considerable increase in price. Phenobarbital has the advantage of being easy to administer. After the optimum dose has been ascertained, patients may continue treatment for months or years with little supervision. The side-effects of this drug are a scarlatina-like generalized rash, in the rare person who is allergic to it, or loss of mental alertness if the dose proves excessive. Individual reactions vary widely. Some patients experience uncomfortable drowsiness with as little as one-half grain a day, whereas other patients can take as much as six or eight grains without noticeable effect. The drug may be used daily for many years without ill effect and without the establishment of habit. The amount may need to be increased from time to time. When taken in huge amounts by mistake or in suicidal attempts, the person experiences extreme ataxia and deep sleep amounting to coma. Phenobarbital is dispensed in tablets containing  $\frac{1}{4}$ ,  $\frac{1}{2}$  or  $1\frac{1}{2}$  grains (0.015, 0.03 or 0.1 gm). For daily oral use the average adult dose is  $1\frac{1}{2}$  grain (0.1 gm) which may be divided between

morning and evening or taken as a single dose at bedtime. The principle is to build up a certain concentration in the body. The drug is excreted slowly, so that frequent divided doses are neither essential nor oftentimes desirable.

*Phenytoin sodium* (sodium diphenylhydantoinate) is an American discovery, first used by Putnam and Merritt of Boston in 1938.<sup>6</sup> A trade name is *dilantin sodium*. This compound, unlike the other two, has little hypnotic effect. On the other hand, administration and dosage require careful supervision because the dose giving full therapeutic effect may approach that at which unpleasant side-effects appear.

The side-effect most frequently encountered is muscular incoordination, expressed as nystagmus, or double vision, unsteadiness in gait, or giddiness. There may also be gastric distress (for which an enteric-coated capsule is available). Two or 3 per cent of patients, those who are allergic to the drug, have a measles-like rash or even a hemorrhagic eruption. Skin eruptions require prompt discontinuance of the drug, though if the skin reaction is mild, gradual reinstatement is often possible. Enlargement of the gums, a frequent complication in children, is not due to vitamin deficiency and can only be minimized by strict oral hygiene and frequent massage of the gums. Overgrowth of hair is seen occasionally in adolescent girls. Rarely there may be loss of weight, drowsiness, fatigue, increased activity, or psychotic-like episodes. The reason for these symptoms in isolated instances has not been demonstrated nor has there been satisfactory explanation for the fact that phenytoin sodium is not equally useful in all types of seizures.

The potentialities of phenytoin sodium have not been fully realized because many doctors suppose that the dosage is similar to that of phenobarbital or they fear side effects. Phenytoin (*dilantin*) sodium is dispensed in sealed capsules containing either  $\frac{1}{2}$  or  $1\frac{1}{2}$  grains (0.03 or 0.1 gm.) For adults the beginning dose is a  $1\frac{1}{2}$  grain capsule taken two or three times a day with meals (and with plenty of water in the event there is gastric distress). The dose is then increased gradually at two- or three-month intervals until either seizures are controlled or unpleasant side effects appear. The dose is maintained at a level which is most effective or is just below the level of unpleasant symptoms. For adults this is three, four or five  $1\frac{1}{2}$  grain (0.1 gm.) doses daily, and for young children a third of that amount. Use over a period of years has not resulted in reported ill effects nor, in general, has there been failure of the drug to hold vantage points which were gained initially. As with phenobarbital, the dosage may need to be increased if the seizures return. For patients who do not experience gastric distress two or more capsules may be taken together for the sake of convenience. When the maximum dose of phenytoin which can be borne, is still not effective, the addition of phenobarbital gives additional benefit in approximately one third of the cases.<sup>6</sup> Such addition, however, does not permit reduction in the amount of phenytoin.

*Mebaral* (n-methylethyl-phenyl barbituric acid), in Europe called prominal, is sometimes used as a substitute for phenobarbital.<sup>7</sup> Dispensed in tablets of  $\frac{1}{2}$  and 3 grains (0.03 or 0.2 gm) from 3 to 9 grains (0.2 to 0.6 gm) may be given daily.

*Amphetamine* (benzedrine) *sulfate* has been advocated in order to offset the sedative effect of anticonvulsants which are hypnotic, or perhaps when alcoholism, behavior or narcolepsy is a complication. The dose is from 5 to 30 mg a day, taken mostly in the forenoon to prevent insomnia.

*Caffeine* can be taken as pills or more pleasantly as coffee, counting 2 grains to the cup. Dosage varies from 5 to 15 grains a day taken with meals. If too stimulating, or if definite results are not observed quickly, large dosage should not be maintained.

*Glutamic acid* is dispensed in large 5 grain (0.33 gm) tablets. The dose per day is 36 tablets (12 gm). The amount is usually limited by gastric distress, allayed somewhat by liberal use of fluid.<sup>8</sup>

*Tridione* (3, 5, 5-trimethyloxazolidine-2, 4-dione, Abbott), described by Richards and associates,<sup>9, 10</sup> is not yet on the market, and will be mentioned under "petit mal."

Other drugs, some of considerable promise in animal observations, are now receiving clinical trial. The report of Merritt<sup>11</sup> indicates the range which has already been covered.

**Different Drugs for Differing Seizures**—For many years quinine was given for all sorts of fever. Now a certain drug is aimed at the cause of the given fever. When only the sedatives bromide and phenobarbital were available, of necessity one of these was given for all types of seizures, whether convulsive or not. Other medicines are now at hand. We know that different kinds of seizures are associated with different wave frequencies (see the figure) and that these frequencies are affected in opposite ways by opposite alterations of brain chemistry. Logically, therefore, a specific chemical should be chosen for the stabilization of specific cortical dysrhythmias and for specific types of seizures. Essential knowledge for doing this is still lacking and we must for the present depend on the method of trial and error. Each case is a therapeutic experiment. Open-minded individuality of treatment is a cornerstone of success. However, much time and grief can be saved by an understanding of which drug is most likely to affect favorably a certain type of seizure.

**JACKSONIAN AND FOCAL SEIZURES**—In spite of the successful surgical removal of an epileptogenic lesion, supplementary drug therapy may be required. *Phenytoin sodium* is the drug of choice, followed by phenobarbital and bromides. Because pathologic involvement of the brain is present, doses larger than average will be required.

**GRAND MAL**—Here again *dilantin sodium* is the drug of choice, then phenobarbital, mebaral or bromides. If the case is a "fresh" one, and

immediate control of seizures is not essential, phenobarbital is used first because of the ease of handling and the relative infrequency of side effects

Control of status epilepticus (repeated convulsions) imposes particular difficulties. The patient is of course in bed and, if the condition has persisted more than six or eight hours, he has been given a cleansing enema and is receiving normal saline or 5 per cent glucose solution intravenously. As for anticonvulsants, 3 grains (0.2 gm) of soluble phenobarbital (sodium luminal) dissolved in 10 cc. of water may be given parenterally three or four times in twenty-four hours. Long-lasting narcosis must be avoided. Paraldehyde has the advantage of brief action. From 4 to 8 cc. are injected intramuscularly or very slowly intravenously, stopping when cyanosis appears. If exhaustion threatens, the force of convulsions can be blunted by etherization or possibly by injection of curare (the last named is still experimental and is not here recommended).

**PSYCHOMOTOR SEIZURES**—*Phenytoin sodium* is not only the best drug, it is for most patients the only one for this type of seizure and is to be used without preliminary trial of phenobarbital. The latter drug, given in large amounts, in some cases seems actually to induce or prolong the amnesic or psychotic-like episodes. If the patient proves sensitive or allergic to the drug, or if it doesn't control, phenobarbital should be tried, perhaps with the addition of amphetamine (benzedrine) sulfate to combat drowsiness, if the required dose of phenobarbital is large.

**PETIT MAL, MYOCLONIC JERKS AND AKINETIC SEIZURES**—These three manifestations may be grouped together since in each the cortical dysrhythmia, when present, is of the alternate wave and spike variety. However, persons, usually children, with akinetic seizures are more likely to have the slower, two per second formation in the routine record. Thus, unlike the three per second variety, is not easily influenced by alterations of blood alkalinity, carbon dioxide, glucose or oxygen. Also, the akinetic seizures more often have a background of pathology than the petit mal.

The *ketogenic diet* is of definite value in many cases of petit mal. Phenytoin sodium may increase petit mal, and only the occasional patient with one of these three forms of epilepsy is helped by phenytoin sodium, phenobarbital or mebaral, although each of these drugs is worth a trial, in order to discover that occasional patient.

In a minority of patients I have observed beneficial results in petit mal or myoclonic jerks from the daily administration of 10 to 15 grains of *caffeine* without other therapy. Most patients, however, either are not helped or are too stimulated to continue. Most striking has been the case of one young man with myoclonus epilepsy whose jerks are so frequent and violent that for years he has been unable to

work on those days in which he does not drink from five to ten cups of coffee. Intravenous injection of 0.5 gm of caffeine sodium benzoate stops at once both the jerks and the wave and spike formations of the electroencephalogram.

Price, Waelsch and Putnam<sup>8</sup> in 1943 reported six cases of petit mal and two of psychomotor seizures in which the addition of *dl*-glutamic acid to the patient's other medication improved both the seizures and the dispositions of patients. At first the authors believed benefit was due to an acidifying action of the drug, but later experience disproved this. Until results on a larger series of cases, and by other authors are reported, glutamic acid must remain as another "something that might be tried."

*Amphetamine (benzedrine) sulfate* has received favorable mention in the treatment of petit mal in children.

*Tridione* (3, 5, 5-trimethyloxazolidine-2, 4-dione, Abbott) in my experience has had the most decisive inhibitory effect on petit mal (pykno-epilepsy), myoclonic jerks and akinetic seizures of anything so far tried. The experience has been too short to judge of the long-term effects, either in stopping seizures or in producing unpleasant side effects. Also, the medicine cannot be ready for the market for some time.

I have given this drug to thirty patients who were having petit mal (pykno-epilepsy) very frequently, five to fifty attacks daily, which had not been helped by one or the other of dilantin, of phenobarbital or of glutamic acid. Because petit mal recurs many times a day the immediate results of therapy can be seen quickly, but in judging effects caution is required because of the fact that petit mal tends to disappear spontaneously before adulthood is reached. These thirty patients have taken tridione for a period of from one to twelve months. Petit mal, myoclonic jerks or akinetic seizures have disappeared or practically disappeared in two-thirds. Nearly all experienced some improvement, but in some the intervention of side effects (skin eruptions, nausea or sensitiveness to light) prevented continued use. An unexpected, but welcome, feature in several cases has been the failure of seizures to return after the drug was discontinued. These observations on the effect of 3, 5, 5-trimethyloxazolidine-2, 4-dione on the three types of seizures are only preliminary, and are mentioned here principally to illustrate the point that drug therapy in epilepsy is a fertile field which has not yet been adequately tilled.

**MIXED SEIZURES**—The patient who has both grand mal and petit mal presents a dilemma, for the best remedy for grand mal (phenytoin sodium) may aggravate petit mal. In the presence of grand mal, petit mal may be disregarded and phenytoin sodium prescribed, phenobarbital may straddle the dilemma, or a combination of phenytoin sodium and one of the drugs effective for petit mal may be tried. Only patient testing will give the right answer for the individual patient.

This section on therapy may end with mention of the most potent of remedies, that supplied by nature. Brain waves become more stabilized, seizures tend to become fewer as the person grows older.

**Social and Psychological Treatment**—The physician who examines and prescribes medicine for his epileptic patient has discharged only half of his responsibilities. Efforts to control attacks are indeed the substantial core of the treatment, but attention must be paid to the doubts and fears which both possess and surround the patient: fear of the seizure, which strikes without warning, fear of what people will say, of losing his friends and his job, of losing his mind, of never losing these horrible convulsions. First the patient must be "strengthened in the inward man," given perspective, hope, courage and the will to win. Parents, family and friends must be coached as to the proper measures and attitudes: quiet and frank helpfulness without show of undue anxiety or the imposition of unnecessary restrictions, but with assistance in gaining an education and in maintaining employment and normal social relationships. A popular exposition of the essential facts about epilepsy and its treatment is in book form.<sup>12</sup>

The physician must evaluate the strength of the materials with which he has to build. Some patients are carefree to the point of neglecting medication and are impervious to the implications of their condition. Others who may be much more lightly affected are so discouraged and burdened with fear and shame that words of hope fall on thickened eardrums. Parents may be selfish and thoughtful only of their own convenience and social position or they may be overfearful and solicitous to the point of neutralizing the best efforts of the doctor. In most cases parents and other relatives are sufficiently intelligent and cooperative so that a forward-looking program can be carried out. In a well ordered hospital or clinic, social workers are of great help. Treatment of the whole person and not just his seizures is expensive of time, but in the end rich rewards accrue to the physician who counts his income in grateful friends as well as in dollars. Physicians who follow their patients from youth into manhood and womanhood, as I have, will realize with relief that time is on the side of the patient, that seizures tend to get better, rather than worse, with the passing years.

The further one gets from the family circle the more difficult are the adjustments. Children of school age encounter ignorance and prejudice among teachers and the parents of other students. Parents must make contact with principal and teachers and secure their cooperation, backed if necessary by a note from the doctor. Continuance in school when attacks are infrequent, is a part of the treatment for most youngsters. The exceptional child who is overconscientious or excitable or nervous about his work may need to be taught at home.

Exercise of the mind is as important a therapeutic agent as many of the drugs in common use. Activity of nerve cells results in production



TYPES OF SEIZURES, ELECTROENCEPHALOGRAPHIC PATTERNS AND THERAPY

Type of Seizure	Chief Characteristic	Electroencephalogram		Therapy In Order of Choice
		In Seizure	Interseizure	
Jacksonian	"March" of sensation or motion, consciousness retained	High voltage fast discharge beginning locally and spreading	Usually normal.	Surgical removal of discharging focus Phenytoin sodium. Phenobarbital or others.
Focal convulsion	One-sided convulsion or localized symptoms initiating generalized convulsion—consciousness lost	High voltage fast waves beginning locally	Focus of seizure discharge or swaying baseline.	Possibly neurosurgery Phenytoin sodium. Phenobarbital or others.
Grand mal	Generalized tonic-clonic convulsion, consciousness lost	Generalized continuous high voltage fast waves or spikes	Seizure discharge—17% Waves slow or fast—64% Normal—18%	Phenytoin sodium. Phenobarbital or others.
Psychomotor (psychic equivalent)	Period of amnesia, with or without tonic muscular spasm or contractions	Generalized high voltage slow waves, perhaps square topped.	Seizure discharge—49% Waves slow or fast—36% Normal—15%	Phenytoin sodium
Petit mal (pykno-epilepsy)	Transient lapse of consciousness, minimal rhythmic jerking at three per second	Generalized high voltage dart and dome at 3 per second	Dart and dome—82% Other abnormalities—10% Normal—8%	Ketosis Tridione, Caffein Glutamic acid Mebal or others
Myoclonic jerks	Lightning like jerk of extremities, with consciousness probably retained.	If anything, single petit mal dart and dome	Possibly isolated dart and dome	Same as for petit mal
Akinetic	Sudden loss of posture with falling or nodding	Often series of high voltage 2 per sec. slow spike and wave—frequently localized—pronounced dysrhythmia and oftentimes not accompanied by clinical symptoms.		Tridione Phenobarbital or others

of carbon dioxide and acidosis which tends to inhibit the abnormal electrical discharges which are the inward expression of observable seizures. For practical reasons also education and training are assets which tend to counterbalance the liability of seizures.

For those beyond school age, employment is important not only for the individual and society, but also for maintenance of morale and for its anticonvulsant influence. Muscular and mental activity is a therapeutic agent, a fact which needs to be continuously reiterated because for generations the dictum has been "quiet and rest."

The physician also has responsibility for the education of fellow physicians and the general public. He should encourage many of his patients to join the American Epilepsy League which has its headquarters at 50 State Street, Boston. By joining with others similarly situated, the patient and his family and friends can aid in the important task of breaking down public prejudice, and in encouraging the medical research which is essential for continued gains against epilepsy. Physicians who have a continuing interest in this subject should also join the American Chapter of the International League Against Epilepsy\* which, jointly with the American Epilepsy League, publishes the magazine, "Epilepsia." The broader and more numerous the fighting points established against epilepsy the sooner will it be conquered.

### CONCLUSIONS

Epilepsy is no more enigmatic than diabetes or extrasystoles or old age. Sometimes neurosurgery, and always mental hygiene, are important aids to treatment, but success depends much on skill and individuality in the administration of drugs. Epilepsy is a chemical disorder to be treated in the main with chemical means. The different types of seizures—jacksonian, focal, grand mal, psychomotor petit mal (pykno-epilepsy), myoclonic and akinetic—may require different surgical or medical treatment. A new medicine, tridione, which is not yet on the market, promises help for most patients whose seizures are of the petit mal (alternate spike and wave) variety. Most patients who are treated as individuals, with consideration for the type of seizure and for the complicating psychological and social problems can be made relatively free of seizures and of fear.

### BIBLIOGRAPHY

- 1 Gibbs, F. A., Gibbs, E. L. and Lennox, W. G. Electroencephalographic Classification of Epileptic Patients and Control Subjects. *Arch Neurol & Psychiat.*, 50 111 (Aug.) 1943
- 2 Lennox, W. G., Gibbs, E. L. and Gibbs, F. A. Inheritance of Cerebral Dysrhythmia and Epilepsy. *Arch Neurol & Psychiat.*, 44 1155 (Dec.) 1940
- 3 The Brain Wave Pattern, An Hereditary Trait. *Jour of Heredity* In press  
Secretary: Dr. F. A. Gibbs, Illinois Neuropsychiatric Institute, Chicago Illinois.

- 4 Penfield, W and Erickson, T C *Epilepsy and Cerebral Localization* Springfield, Illinois, Charles C Thomas, 1941
- 5 Merritt, H H and Putnam, T J Sodium Diphenylhydantoinate (Dilantin Sodium) in the Treatment of Convulsive Disorders *J A M.A.*, 111 1068, 1938, *Arch Neurol & Psychiat.*, 42 1053, 1939
- 6 Merritt, H H and Brenner, C Sodium Diphenyl Hydantoinate (Phenytoin Sodium) and Phenobarbital Combined *J Nerv & Ment Dis*, 96 245 (Sept ) 1942
- 7 Cohen, B and Myerson, A Mebaral in the Treatment of Epilepsy *New England J Med*, 227 336 (Aug 27) 1942
- 8 Price, J C., Waelseh, H and Putnam, T J dl-Glutamic Acid Hydrochloride in Treatment of Petit Mal and Psychomotor Seizures *J A M.A.*, 122 1153 (Aug 12) 1943
- 9 Richards, R K and Perlstein, M A Tridione, A New Experimental Drug for the Treatment of Convulsive and Related Disorders *Chicago Neurological Society Arch Neurol & Psychiat* (in press)
- 10 Everett, G M and Richards, R K Comparative Anticonvulsive Action of 3, 5, 5-Trimethyloxazolidine-2, 4-dione (Tridione), Dilantin and Phenobarbital *Pharmacol & Exper Therap.*, 81 402 (Aug ) 1944
- 11 Merritt, H H Experimental Testing of Antieconvulsant Action of Various Drugs *Epilepsia* (in press)
- 12 Lennox, W G *Science and Seizures, New Light on Epilepsy and Migraine* New York, Harper & Brothers 1941

# THE TREATMENT OF NONHEMOLYTIC STREPTOCOCCUS SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN

DONALD G. ANDERSON, M.D. • AND CHESTER S. KEEFER, M.D., F.A.C.P.†

UNTIL very recently, few diseases have presented a more hopeless prognosis than has subacute bacterial endocarditis. Prior to the introduction of the sulfonamides no effective treatment was known and the mortality rate exceeded 99 per cent. It is now recognized that the advent of sulfonamide therapy marked the beginning of a new era in the treatment of this disease. For the first time, adequate evidence was provided that this disease could be cured by the administration of a specific chemotherapeutic agent. Unfortunately, the number of patients permanently benefited by sulfonamide therapy was disappointingly small, since not more than 5 per cent of all those treated recovered. Thus, while the sulfonamides established the principle that subacute bacterial endocarditis could be cured, the need for an even more potent chemotherapeutic agent for the treatment of this disease soon became clear.

During the last year and a half experience has been accumulating to indicate that in penicillin a chemotherapeutic agent is now available that will make possible the successful treatment of approximately 75 per cent of patients with subacute bacterial endocarditis caused by nonhemolytic streptococci. At this time we propose to review some of our experiences with the use of penicillin in the treatment of this disease. Before taking up the problem of treatment, however, we shall review briefly the more important facts that are known concerning the incidence, etiology, pathogenesis, and clinical course of subacute bacterial endocarditis.

**Incidence**—Subacute bacterial endocarditis is not a rare disease. Post-mortem studies have shown that approximately 25 per cent of all adult patients with rheumatic heart disease die of it. The incidence of the disease in patients with congenital anomalies of the heart and

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston. The penicillin was provided by the Office of Scientific Research and Development from supplies assigned by the Committee on Medical Research for clinical investigations recommended by the Committee on Chemotherapeutics and Other Agents of the National Research Council.

• Instructor in Medicine, Boston University School of Medicine Research Fellow in Medicine, Evans Memorial Massachusetts Memorial Hospitals.  
† Wade Professor of Medicine Boston University School of Medicine Director Evans Memorial, and Physician-in-Chief Massachusetts Memorial Hospitals Chairman, Committee on Chemotherapeutics and Other Agents, Division of Medical Sciences, National Research Council

great vessels is probably at least as high. In any moderate-sized hospital with an active medical service in areas where rheumatic heart disease is prevalent, it is not unusual to encounter annually at least five or ten patients suffering from this disease.

**Etiology**—It is well known that this disease is usually caused by organisms of low virulence. The organism encountered in about 95 per cent of all cases is the nonhemolytic streptococcus, various species of which are normal inhabitants of the oral cavity and the gastrointestinal tract of man. Many of these species produce a greenish discoloration when grown on blood agar. Such organisms have been commonly referred to as streptococcus viridans (alpha hemolytic streptococci). Other species produce no alteration in the blood and have been termed indifferent streptococci (gamma streptococci). Rosebury has reviewed the recent attempts to arrive at a more precise classification of nonhemolytic streptococci, and his article may be profitably consulted by those who are interested in this problem.

Occasionally other organisms of low virulence are found to be the cause of subacute bacterial endocarditis. Included in this group are *Hemophilus influenzae*, the various members of the *Brucella* group, the members of the genus *Neisseria*, *Staphylococcus albus*, and *Streptobacillus moniliformis*.

**Predisposing Factors**—With rare exceptions, subacute bacterial endocarditis occurs only in patients with preexisting valvular heart disease. Thus, about 80 per cent of cases occur in patients with rheumatic heart disease. It is well known that patients who have had only one or two attacks of acute rheumatic fever, who have never suffered from marked congestive heart failure, and who have not developed auricular fibrillation are the rheumatic subjects most likely to develop subacute bacterial endocarditis. There seems little doubt that the acquiring of this disease is an accident that significantly shortens the life of just those patients with rheumatic heart disease who might otherwise have the best prognosis for longevity. The studies of Juca and White have demonstrated that the interval between the first attack of rheumatic fever and death is shorter in patients dying of subacute bacterial endocarditis than in any other group of adult patients with rheumatic heart disease.

Next in order of frequency the disease is encountered in patients with congenital anomalies of the heart or great vessels. Occasional cases are seen in which the preexisting valvular lesion is due to syphilitic involvement of the aortic valve, even less common are cases in which the only abnormal changes in the valves are those due to atherosclerosis.

Perhaps the best explanation as to why this disease occurs almost entirely in patients with preexisting valvular lesions is that advanced by Grant. By means of careful postmortem studies he demonstrated that minute platelet and fibrin thrombi can usually be detected on the

surface of the heart valves of patients with rheumatic and congenital valvular lesions. Normal valves, on the other hand, rarely show these thrombi except in an occasional patient who has undergone a long, debilitating illness. Grant postulated that such fibrin thrombi serve as a focus in which bacteria that gain transient access to the blood stream may become lodged and multiply and thus give rise to a typical bacterial vegetation. In normal hearts bacteria find no such prepared lodgment, and as a result they are eliminated by the normal antibacterial activity of the blood without having an opportunity to gain a foothold and multiply.

**Pathogenesis**—When the predisposing factors mentioned in the preceding section are present the critical point in the pathogenesis of subacute bacterial endocarditis becomes the mechanism whereby bacteria gain access to the blood stream and thus secure the opportunity to localize on the heart valves. It is now appreciated that transient, asymptomatic bacteremias are much commoner than was once supposed. Thus, it has been demonstrated that in the first five minutes after tooth extraction in 15 to 70 per cent of patients various organisms, most frequently nonhemolytic streptococci, can be cultured from the circulating blood. The poorer the condition of the patient's gums the more likely is bacteremia to occur. Simple massage of the gums or vigorous mastication may at times be sufficient to give rise to bacteremia. After tonsillectomy, after abdominal operations, or after manipulative procedures involving the genitourinary tract transient bacteremia may also be detected, although with less frequency.

Once attention was directed to the possible role that such episodes might play in the pathogenesis of the disease, it was not long before physicians began to report cases of subacute bacterial endocarditis in which the onset of the disease could be definitely associated with one of the precipitating incidents that have been mentioned. Careful history taking has revealed that in no less than 25 per cent of patients who develop subacute bacterial endocarditis the onset of symptoms follows closely the extraction of one or more teeth. In a smaller group of patients, the disease has been shown to follow other operative procedures or uncomplicated upper-respiratory infections. While our knowledge of the precipitating factors is increasing, it must be acknowledged that in more than half the patients with subacute bacterial endocarditis even the most careful history fails to reveal the initiating injury that produced the bacteremia.

**Clinical Manifestations**—The symptomatology of subacute bacterial endocarditis is essentially that of a chronic infection, the gradual downward course of the illness being punctuated from time to time by embolic episodes of lesser or greater magnitude. The duration of the disease varies from a few weeks to more than a year. The average duration in untreated cases is approximately six months.

The classical picture presented by a moderately advanced case is a

familiar one and is easily recognized. The patient is listless and wasted. There is fever, usually of the remittent type, and night sweats may be severe. Pallor is marked. Clubbing of the fingers and toes is common. Petechiae are found in the conjunctivae, ocular fundi, oral mucosa, and skin. Osler's nodes may be present, as well as splinter hemorrhages beneath the nails. The examination of the heart almost always reveals the signs of antecedent valvular disease. The spleen is usually palpable. Embolism produces severe pain or marked disturbances in function of the involved part.

Such well known manifestations of the disease require no special comment. During the early weeks of the infection, however, the pathognomonic stigmata of subacute bacterial endocarditis are frequently absent, and Christian has recently directed attention anew to the fact that the presenting symptoms during the early phase of the disease may be quite nonspecific. In reviewing a large series of cases, he found that in 52 per cent the earliest symptoms were malaise and fever, in 32 per cent joint or muscle pains, and in 16 per cent nausea or loss of appetite. In the majority of these cases the correct diagnosis was not made until the disease was moderately far advanced. Among the incorrect diagnoses that were entertained for longer or short periods were those of influenza, grippe, typhoid fever, tuberculosis, undulant fever and acute rheumatic fever.

Christian has rightly urged that in any patient with valvular heart disease who has fever lasting more than one week that has not been fully explained, the diagnosis of subacute bacterial endocarditis should be strongly suspected and a blood culture be obtained.

**Complications**—The complications of the primary disease that may occur in subacute bacterial endocarditis are too numerous to be reviewed in detail. Large emboli may seriously impair the function of any organ. Three important complications may be briefly mentioned. The implantation and subsequent proliferation of bacteria on the walls of the large or small arteries may occur and result in the production of *mycotic aneurysms*. Such aneurysms may rupture and give rise to a fatal hemorrhage.

Pathologic changes in the kidney are encountered with great regularity. Usually the lesion is of the focal embolic type and has no significant effect on renal function. In 10 to 20 per cent of cases, however, a true *diffuse glomerulonephritis* develops, and in such instances signs of impaired renal function appear and the patients not infrequently die in uremia. For reasons that are not at present clear, this complication is most apt to occur in so-called "bacteria-free" cases.

A *diffuse myocarditis* apparently due to the embolization of the small branches of the coronary arteries may occasionally be present, and if extensive may give rise to the development of severe congestive heart failure. Although not an actual complication of the bacterial infection, it should be recalled that acute rheumatic myocarditis also

may and frequently does exist concomitantly with subacute bacterial endocarditis

**Diagnosis.**—The diagnosis of subacute bacterial endocarditis is most firmly established by culturing the infecting organism from the blood. In patients who present typical clinical findings two positive blood cultures may be considered sufficient to substantiate the diagnosis. In more obscure cases the diagnosis is made with more certainty when the same organism is recovered in three or more cultures.

In 85 to 90 per cent of cases the physician can recover the organism from the blood without difficulty. Incubating the cultures in an atmosphere containing an increased concentration of carbon dioxide often facilitates the growth of nonhemolytic streptococci. A simple candle jar will usually provide a sufficiently high carbon dioxide concentration for this purpose.

In 10 to 15 per cent of cases, however, it is well known that repeated cultures of the blood fail to reveal the presence of organisms, although bacteria can be readily cultured from the vegetations on the valves at autopsy. Such cases have been called "bacteria-free" cases. Two explanations have been advanced to account for the failure to recover the organisms from the blood during life. One is that the high antibody titer of the blood that is usually present in this disease results in the death of the bacteria as soon as they are swept out into the circulating blood, the organisms that remain in the vegetations being protected from the bactericidal action of the blood by the surrounding meshwork of fibrin. The other explanation for the occurrence of "bacteria-free" cases is that the organisms that are liberated from the vegetations are so few that they escape detection in the blood culture.

In "bacteria-free" cases the diagnosis must be made from the clinical findings. It is important that this necessity be recognized, since otherwise such cases may be deprived of effective treatment.

#### GENERAL CONSIDERATIONS REGARDING PENICILLIN THERAPY

**Susceptibility of Nonhemolytic Streptococci to Penicillin.**—It is well known that penicillin is selective in its antibacterial action, being quite potent against certain organisms and having little or no effect against others. As in other infections penicillin can be expected to be effective in the treatment of subacute bacterial endocarditis only when the infecting organism is susceptible to the action of the drug.

Fortunately, it has been shown that most species of nonhemolytic streptococcus are susceptible to penicillin. More than 90 per cent of the organisms so far tested have been completely inhibited in vitro by concentrations of 0.1 unit or less of penicillin per cubic centimeter. It should be noted, however, that enterococci have usually shown a high degree of resistance to penicillin and may not be inhibited by concentrations of penicillin of five units or more per cubic centimeter.



**Mechanism of Action**—In the treatment of disease, therapy is most effective when the precise mechanism whereby an agent effects recovery is understood. Such knowledge makes possible the planning of a rational program of treatment. Our understanding of the manner in which penicillin acts in subacute bacterial endocarditis is still incomplete.

Two possible mechanisms of action may be suggested. One of these takes into account the natural tendency toward the organization and fibrosis of vegetations that is observed even in untreated cases of subacute bacterial endocarditis. It is possible that the prolonged administration of penicillin in adequate doses inhibits the growth and multiplication of bacteria on and near the surface of the vegetations, while granulation tissue growing up from the base of the vegetation and endocardium growing over its surface result in healing of the lesion. It is conceivable that if healing occurs in this manner, the "healed" lesion may contain bacteria that remain viable for a period of time but are well walled off and therefore incapable of causing further injury.

Such a mechanism is in accord with the observed clinical fact that although treatment with penicillin in most cases of subacute bacterial endocarditis renders the blood culture sterile within twenty-four to forty-eight hours, if treatment is not continued for a period of weeks, the blood culture again becomes positive within a short time after penicillin is withdrawn.

The second possible mechanism that can be suggested is that penicillin penetrates all parts of the vegetation and sterilizes the lesion by killing all bacteria present. In support of this mechanism evidence can be advanced that high concentrations of penicillin in vitro have a bactericidal action. The dosages usually employed in the successful treatment of subacute bacterial endocarditis, however, do not provide concentrations of the drug sufficiently high to produce such an action. Even if such large doses were used, it is doubtful that the drug could penetrate the dense masses of fibrin commonly encountered in vegetations.

While it cannot be denied that this second mechanism may at times be operative, since clinical experience with the administration of very large doses of penicillin over short periods of time has been limited, the observations to date indicate that the inhibition of the organisms present in the vegetations for a period of time sufficient to permit the organization and endothelialization of the lesion is the more likely explanation for the manner in which penicillin effects recovery in subacute bacterial endocarditis.

**General Outline of Treatment**—Because not all species of nonhemolytic streptococcus encountered in subacute bacterial endocarditis are sensitive to penicillin, it is important at the outset of treatment to test

each patient's organism for its sensitivity to the drug. This test can be easily performed by a slight modification of the method described by Rammelkamp and Maxon.

In this procedure, a standard solution of penicillin containing 20 units per cubic centimeter is prepared by suitably diluting one of the preparations of penicillin that are available for therapeutic purposes. Fifteen small sterile test tubes are placed in a rack and into each tube 0.5 cc. of nutrient broth is pipetted. To the first tube 0.5 cc. of the standard solution is added, and after thorough mixing serial dilutions are made in the usual manner.

The inoculum of the organism to be tested is prepared by diluting a twenty-four hour culture so that the inoculum contains between 10,000 and 100,000 organisms per cubic centimeter. After the dilution has been made, defibrinated horse or rabbit blood is added to give a final concentration of 1 per cent. Five tenths of a cubic centimeter of the inoculum is then pipetted into each test tube. The tubes are shaken well and incubated for eighteen to twenty-four hours, at the end of which time the tubes are examined for gross evidence of growth. Subcultures are made on blood agar from several tubes near the end point—that is, the tube with the lowest concentration of penicillin that shows no growth.

The test is read by determining the tube containing the least penicillin in which no growth is obtained on subculture. The amount of penicillin in this tube represents the minimum concentration of penicillin per cubic centimeter that will just completely inhibit the growth of the organism tested.

This simple test can be performed by any bacteriologic laboratory. Since its performance requires a minimum of seventy-two hours after the organism has been isolated from the blood culture, the physician may prefer to begin treatment once the diagnosis has been established and later make such modifications in dosage as the results of the sensitivity test indicate.

**Dosage.**—Clinical experience has demonstrated that in patients whose organisms are inhibited by 0.1 unit or less of penicillin per cubic centimeter a daily dosage of 200,000 units is usually adequate. However, now that penicillin is freely available, it appears to be safer to use a slightly higher dosage, although in most cases there seems to be little reason to increase the dosage beyond 300,000 units a day. In patients whose organisms are less sensitive to penicillin considerable experimentation is frequently necessary to find a dosage that will sterilize the blood.

**Methods of Administration.**—While we have employed various methods of administration, it is our present belief that the *intermittent intramuscular method* is the most satisfactory and convenient one. When this method is used, the total daily dose is divided into equal doses that are given every two or three hours throughout the day and night. By using a penicillin solution of high concentration—for example, 25,000 units per cubic centimeter—the volume of the individual doses can be kept small and the discomfort caused by the injections be reduced to a minimum.

We have also employed continuous intravenous and continuous in-

intramuscular infusions in our studies. At the moment we do not believe that they offer any particular advantage. They are difficult to regulate, and necessarily result in a certain degree of immobilization of the patient.

**Duration of Treatment.**—From our experience it is our belief that treatment should be continued for a minimum of two weeks and preferably for three after the blood culture has become sterile. In a few cases more prolonged treatment has been necessary. In such cases it has been our feeling that either the size of the vegetations or peculiarities in the histology of the lesions have produced a delay in organization and endothelialization that has made necessary the longer periods of treatment.

**Other Specific Therapeutic Measures.**—There is as yet no experience that indicates whether the simultaneous administration of one of the sulfonamides with penicillin is of any value. This problem cannot be satisfactorily evaluated until more is known about the effect of penicillin therapy alone in the treatment of this disease. The same can be said for the use of artificial-fever therapy.

Regarding the use of anticoagulants such as heparin or dicumarol, sufficient evidence has accumulated to indicate that these agents do not enhance the action of penicillin and that the results obtained when these agents are used are no better than when penicillin alone is given. It is also well known that the use of these agents may be hazardous. It may be said, therefore, that anticoagulants have no further place in the treatment of subacute bacterial endocarditis.

**Supportive Treatment.**—Patients with subacute bacterial endocarditis, especially those seen late in the disease, present many of the features of chronic illness that require careful management. If the patient is having high fever, bed rest is advisable. In other cases the degree of activity allowed may be adjusted to the patient's strength. Patients who have lost weight should be provided with a nourishing diet, and in those with severe anemia blood transfusions may be indicated.

The use of digitalis and the restriction of the salt and fluid intake may be necessary in patients who show signs of a cardiac failure.

The careful management of convalescence in patients who recover from the infection is of the greatest importance. When treatment has been completed, even though the blood culture remains sterile and the vegetations may be assumed to have healed, the majority of patients still suffer from the residual effects of the chronic debilitating illness through which they have passed. In most instances several weeks, or more often several months, of convalescence are required before the patient has fully recovered his strength and energy. It is important, therefore, that his activities be regulated during the period of convalescence. If the situation is fully explained to the patient, needless discouragement at his failure to make more rapid progress can be prevented.

## PRESENTATION OF CASES

In the space remaining we propose to present several cases that we have treated, which illustrate the principles that have been enumerated above and that also bring out some of the special problems encountered in the treatment of subacute bacterial endocarditis with penicillin. The first case selected is one of several that have shown rapid and progressive improvement under penicillin therapy

CASE I—K B., a 47 year old woman, had never had a recognized attack of acute rheumatic fever. At the age of 11 she was told that she had a heart murmur. She remained well, without any symptoms referable to the heart except for the occurrence of mild cardiac decompensation during the last trimester of her fourth pregnancy fifteen years before the present illness.

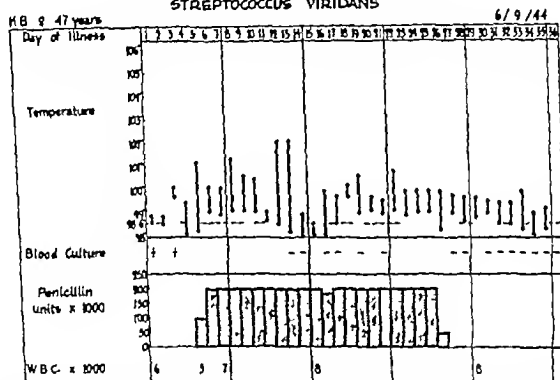
SUBACUTE BACTERIAL ENDOCARDITIS  
STREPTOCOCCUS VIRIDANS

Fig 163 (Case I)—Clinical course of a patient with subacute bacterial endocarditis who responded promptly to treatment. The patient received 25 000 units of penicillin intramuscularly every three hours for twenty-one days. The total dosage was 4,200,000 units. The patient has been followed for one year and has remained well.

Sixteen weeks before admission to the Evans Memorial Hospital, without any known precipitating event, the patient developed generalized muscular aching and malaise. One week later she began to have afternoon fever often as high as 103 F., and severe night sweats. She was gradually forced to reduce her activity and for a month prior to admission she had remained in bed. The patient was not aware of any embolic phenomena. Two weeks before admission she entered another hospital, where the blood culture was found to be positive for *Streptococcus viridans*. She had lost 10 pounds during her illness.

On physical examination the patient appeared pale and chronically ill. There were no signs of cardiac decompensation. No petechiae could be seen in the skin or mucous membranes. There was marked clubbing of the fingers and toes. The

heart was slightly enlarged in the region of the left ventricle. The rhythm was regular. A grade 3 systolic murmur was present at the apex and was transmitted to the axilla. No diastolic murmurs were heard. The pulmonic second sound was accentuated. The spleen was palpable 2 cm below the left costal margin.

Laboratory studies revealed the hemoglobin to be 95 gm, the hematocrit 33 per cent, and the white-cell count 5850, with a normal differential count. The examination of the urine was negative. Two blood cultures were positive for *Streptococcus viridans*. This organism was tested for its sensitivity to penicillin and was found to be completely inhibited by 0.04 units of penicillin per cubic centimeter.

*Course*—The hospital course is shown in Figure 163. Treatment with penicillin was begun on the 5th day and was continued for 21 days. The dosage was 25,000 units, administered intramuscularly every three hours.

Twenty-four hours after the beginning of treatment the blood culture was negative, and it remained negative thereafter. Seventy-two hours after the beginning of treatment the patient felt much better and was aware of an increasing interest in her surroundings.

Despite the fact that a low-grade fever persisted, the symptomatic improvement was progressive. The day after treatment was completed the patient was allowed to sit up in a chair for a few minutes, and thereafter her activity was gradually increased, without ill effect. After treatment was discontinued, the rectal temperature did not go above 100° F, and except for one reading remained below this figure. No embolic phenomena were observed before, during, or after treatment.

The patient was discharged ten days after the completion of treatment. At this time she enjoyed a sense of well-being but still felt weak. Physical examination at discharge revealed no change in the clubbing of the fingers or in the heart murmur. The spleen was barely palpable and remained so for the first month after treatment. Two months after leaving the hospital the patient had regained her normal weight and was beginning to do light housework. By the fourth month the patient had fully recovered her strength and had resumed all her normal activities. During the last eight months she has felt entirely well. In this time the clubbing of the fingers has gradually receded and is now barely detectable. Frequent blood cultures have been taken during the year that has elapsed since treatment was completed. They have all been negative.

In summary, this patient had had known valvular heart disease for thirty-six years but had remained well, except for a brief episode of cardiac decompensation, until the onset of the symptoms of subacute bacterial endocarditis at the age of forty-seven. Treatment with penicillin was begun sixteen weeks after the development of the first symptoms. The total dosage of penicillin was 4,200,000 units, given over a period of twenty-one days. The blood culture became permanently negative twenty-four hours after treatment was begun, and the patient noted definite subjective improvement forty-eight hours later. A low-grade fever persisted until treatment was discontinued, and the spleen remained palpable until one month later. The patient had recovered her full strength and had returned to her normal activities four months after the completion of treatment. She has remained well for a period of one year.

Four of our other patients have shown a similar prompt response to the schedule of treatment followed in this case, and have remained

well now for periods varving from eight to sixteen months. While it is still too early to arrive at any final conclusions, the experience to date indicates that roughly half of the patients with subacute bacterial endocarditis caused by nonhemolytic streptococci respond to treatment in the same satisfactory fashion as did the patient that has just been presented. In the other roughly 50 per cent of cases the response is not so satisfactory and more difficulties are encountered. We shall devote the rest of this paper to discussing the cases that we have treated who have presented particular problems.

The next case is that of a patient who while apparently making a satisfactory response to penicillin therapy died suddenly on the ninth day of treatment.

**CASE II**—M. W., a 38 year old woman, had had a single attack of acute rheumatic fever at the age of 13. Following this attack she developed the signs of mitral stenosis, but had no symptoms of cardiac decompensation and remained well until the onset of the present illness.

Six weeks before admission, the patient began to lose her appetite and noticed increasing fatigability. There was no known antecedent illness or operation. The patient continued to work as a secretary until three weeks later when she became aware of fevershiness in the afternoon and developed mild night sweats. These symptoms continued. Three days before entry a blood culture was obtained and was found to be positive for *Streptococcus viridans*. On the day before admission there was a sudden appearance of numbness and weakness of the fingers of the left hand. The patient had lost 10 pounds in weight during her illness.

On physical examination the patient appeared to be only slightly ill. The skin was moderately pale. One petechia was seen on the abdomen. Examination of the heart revealed slight enlargement in the region of the left ventricle and pulmonary cone. The rate was rapid, the rhythm was regular except for occasional premature beats. Presystolic and systolic murmurs were heard at the apex. The pulmonic second sound was accentuated. There were no aortic murmurs. The lungs were normal. The liver and spleen could not be felt. There were no signs of cardiac decompensation. There was moderate weakness of the left hand and fingers. The deep tendon reflexes were hyperactive and equal. There were no pathologic reflexes. There was no clubbing of the fingers or toes.

Laboratory studies showed the hemoglobin to be 10 gm., the red cell count 3,400,000, and the white cell count 13,000, with 80 per cent polymorphonuclear leukocytes. Urinalysis was negative except for a few red blood cells in the centrifuged sediment. The nonprotein nitrogen was 28 mg. per 100 cc. Daily blood cultures during the first 4 hospital days were positive for *Streptococcus viridans*, the colony counts varying from 11 to 24 colonies per cubic centimeter. This organism when tested for its sensitivity to penicillin was found to be completely inhibited by 0.04 units per cubic centimeter.

**Course**—During the first four hospital days the temperature was continually elevated above 101° F., spiking to 103° or 104° each evening. On the fifth day treatment with penicillin was begun, 200,000 units being administered in each twenty-four hour period by means of a slow constant intravenous infusion. The total twenty-four hour volume of the infusion was 2000 cc.

Within twenty-four hours after the beginning of treatment the temperature became normal and it remained normal thereafter. A blood culture taken at this time was still positive but forty-eight hours after the beginning of treatment the

blood culture became negative Daily blood cultures thereafter showed no growth

Coincident with the fall in temperature the patient noticed progressive subjective improvement Her course continued to be extremely encouraging until the afternoon of the ninth day of treatment, when she suddenly complained of a severe headache and began to vomit Within an hour she became comatose, and four hours later respirations ceased A lumbar puncture performed two hours before death revealed a grossly bloody spinal fluid

The important postmortem findings were confined to the brain and heart. There was an extensive area of subarachnoid hemorrhage over the right hemisphere connecting with an area of softening in the right temporal lobe containing a fresh blood clot. The vessel responsible for the massive hemorrhage could not be identified

The heart weighed 420 gm The aortic, tricuspid and pulmonic valves were normal The leaflets of the mitral valve were fused, and the free edge of the valve was rolled and thickened Along the entire valve margin was an irregular row of soft, friable, grayish-red vegetations, each approximately 1 mm in diameter In one area on the auricular surface of the valve was an area measuring 2.0 by 1.2 cm that was completely covered with sessile vegetations Cultures of the vegetations were positive for *Streptococcus viridans*

In summary, this patient had been ill for only six weeks when treatment with penicillin was started Her general physical condition was fairly good, and the infecting organism was sensitive to penicillin The response to therapy was satisfactory, and she was making good progress when she suddenly died from a massive cerebral hemorrhage on the ninth day of treatment, presumably the result of a rupture of a mycotic aneurysm of the right middle cerebral artery or one of its branches

So far as could be determined either before or during treatment, there was every reason to expect that this patient would do as well as did the patient in Case I Unfortunately, her favorable course was interrupted by a fatal complication that was not amenable to chemotherapy One may of course reasonably speculate as to whether earlier treatment might not have prevented the development of this complication One may predict, however, that in a fair proportion of patients treatment will not be started until after complications similar to this one have developed Such cases are certain to limit the number of recoveries that can be effected by chemotherapy

Another important point illustrated by this case is that the failure to cultivate the organism from the circulating blood, even over a period of one week, did not mean that the vegetations had been sterilized

Just a week after this patient died, we had another experience that further demonstrated the fact that subacute bacterial endocarditis frequently presents complications that cannot be treated with chemotherapy A 30 year old man with subacute bacterial endocarditis caused by a nonhemolytic streptococcus that was sensitive to penicillin was admitted for treatment after he had had symptoms for eight months As in Case II there was a satisfactory immediate response to treatment, with a clearing of bacteria from the blood stream and a re-

turn of the temperature to normal within twenty-four hours. On the third day of treatment the patient suddenly developed acute cardiac failure with pulmonary edema. Treatment with digitalis and other measures resulted in temporary improvement, but the patient died in cardiac failure three days later.

Occasionally after apparently responding satisfactorily to a course of treatment, a patient suffers a relapse with a return of symptoms and positive blood cultures. Such relapses may occur at any time from a few days to several months after treatment has been completed. In such cases further therapy is indicated. It has usually appeared desirable with the second course of therapy to increase the daily dosage of penicillin and to give a more prolonged course of treatment.

The next case illustrates the successful response to a second course of treatment by a patient who relapsed after the first course. This case is also of interest because on the basis of the history, physical examination and laboratory studies it was impossible to detect any evidence of antecedent heart disease.

CASE III.—H. H., a 63 year old man, had never had any symptoms suggestive of acute rheumatic fever. He had seen his physician for minor complaints at frequent intervals over a period of many years, but no cardiac abnormalities had ever been detected. One month before the onset of the present illness a tooth had been extracted under local anesthesia. Four weeks later the patient became aware of a feeling of increased fatigability but continued with his work. After six weeks of feeling poorly he consulted his physician, who found his temperature to be 99.4° F but could detect no cause for the fever or symptoms. One week later there suddenly developed pain and an area of redness over the dorsum of the left foot. This gradually disappeared. Two weeks later another tender painful spot appeared in the palm of the right hand. The patient had mild chilly sensations at this time, but the temperature was never higher than 100.4° F and was usually less than 100° F.

During the next two months the patient continued to feel weak and tired but kept on with his work. Four months after the onset of the first symptoms a blood culture was obtained and was found to be positive for *Streptococcus viridans*. A second culture taken four days later was also positive, and the patient was admitted to a local hospital, where he received 12,500 units of penicillin (100,000 units a day) intramuscularly every three hours for fourteen days. Blood cultures taken every three days after treatment was begun were negative. The temperature remained below 99.4° F., and the patient noted a definite improvement in well-being. On the eighth day of treatment there was a small embolus in the left fourth toe. At the completion of treatment the patient was discharged. A blood culture taken two days later was negative.

One week after discharge the patient noted a return of malaise and low-grade fever. A blood culture taken two days later was positive for *Streptococcus viridans*. The patient was then admitted to the Evans Memorial Hospital for further treatment. He had lost no weight during this illness.

Physical examination was essentially negative. There were no petechiae in the skin or mucous membranes. The heart was not enlarged, the rhythm was regular, the sounds were of good quality and there were no murmurs. The spleen and liver could not be felt. There was no clubbing of the fingers or toes. The blood pressure was 145/80.



Laboratory studies showed the hemoglobin to be 14.2 gm., the hematocrit 43 per cent, and the white cell count 8900, with a normal differential count. Urinalysis was negative except for a few red blood cells in the centrifuged sediment. The nonprotein nitrogen was 31 mg per 100 cc. The blood Hinton test was negative. An electrocardiogram was normal. Fluoroscopic examination of the heart and a 7 foot roentgenogram of the chest revealed no abnormality of the heart or great vessels. A blood culture taken on admission was positive for *Streptococcus viridans*, with 8 colonies per cubic centimeter of blood. This organism was completely inhibited by 0.04 units of penicillin per cubic centimeter.

*Course*—The hospital course is shown in Figure 164. During the first 72 hours penicillin was administered by continuous intravenous infusion at the rate of 300,000 units a day. This method had to be abandoned at the end of that time

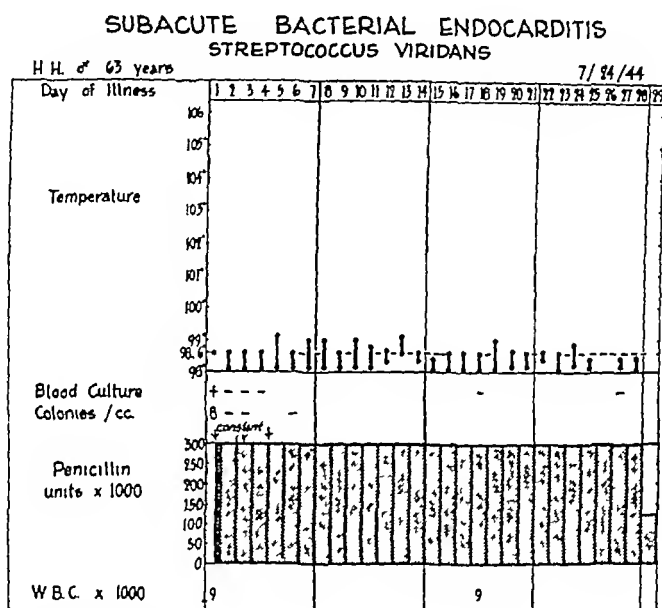


Fig 164 (Case III) —The second course of penicillin treatment in a patient who had relapsed one week after the completion of the first course. Following the second course he has remained well for ten months. This case was of considerable interest because there was no evidence of pre-existing valvular heart disease.

because of the development of a severe thrombophlebitis at the sites of the infusion. For the next twenty-five days penicillin was administered intramuscularly at the rate of 25,000 units every two hours. During the time that intramuscular therapy was given the patient was ambulatory.

The blood culture became negative twenty-four hours after the beginning of treatment and remained negative thereafter. After three days of treatment the patient noted a progressive increase in well-being.

On the day that treatment was completed the patient was discharged from the hospital. During the next two months he gradually recovered his strength completely and at the end of that time returned to full-time work. He has been seen at frequent intervals for the last ten months. Blood cultures have remained negative and there has been no return of symptoms. The examination of the heart is still entirely negative.

This patient's first course of therapy in the light of our present knowledge was obviously inadequate, and one could anticipate that in spite of the temporary improvement relapse would almost certainly occur. The apparently lasting improvement after the second more intensive course of penicillin therapy illustrates the desirability of repeating the treatment in patients who fail to respond to the first treatment, particularly if there is any reason to suspect that the therapy has been inadequate.

This case is also of interest in that it illustrates the mild, insidious course that subacute bacterial endocarditis occasionally pursues, and because so far as we have been able to determine the disease was engrafted on entirely normal heart valves.

The next case presents a slightly different problem from the preceding one. The blood culture became negative after treatment was begun but became positive again even while treatment was being continued.

**CASE IV—D N.**, a 45 year old woman, had never to her knowledge had any of the symptoms of acute rheumatic fever. Two years prior to the onset of the present illness the signs of mitral stenosis were detected on routine physical examination. There had been no symptoms of cardiac decompensation. Ten months before the onset of symptoms a tooth was extracted under local anesthesia.

The patient was in good health until five weeks before admission, at which time she had a shaking chill, followed by a temperature of 103° F. For the next five weeks she had similar episodes of chills and fever at intervals of two to six days. In the intervening period she was afebrile and asymptomatic except for increasing weakness. One episode of fever was accompanied by the appearance of a painful red spot in a fingertip. During the present illness she had lost 20 pounds in weight.

Physical examination showed a middle aged woman who did not appear ill. Examination of the skin revealed 15 or 20 petechiae scattered over the body. The lungs were clear. The heart was enlarged to the left. The rhythm was regular. There was a faint crescendo presystolic murmur and a loud blowing systolic murmur at the apex. There were no aortic murmurs. The liver was palpable 2 cm. below the right costal margin and the spleen 3 cm. below the left costal margin. There were no signs of cardiac decompensation. There was no clubbing of the fingers or toes.

Laboratory studies showed the hemoglobin to be 11 gm., the red cell count 4,000,000 and the white cell count 10,400 with 89 per cent polymorphonuclear leukocytes. Urinalysis revealed a 1 plus albumin and a few red blood cells in the centrifuged sediment. The nonprotein nitrogen was 28 mg. per 100 cc. Five blood cultures taken during the first week were positive for *Streptococcus viridans*. A colony count performed on one occasion showed 68 colonies per cubic centimeter. This organism was tested for its sensitivity to penicillin and was found to be completely inhibited by 0.08 units per cubic centimeter.

**Course**—The hospital course is shown in Figure 165. Treatment with penicillin was begun on the sixth day with a dosage of 25,000 units intramuscularly every three hours. For the first three days after the beginning of treatment the blood culture was negative, but thereafter it again became positive and remained so until the nineteenth day of treatment, when the dosage was increased to 25,000 units every two hours. Again the blood cultures became negative for three days only to become positive once again. After fifteen days the method of administration was changed from intermittent intramuscular injections to a continuous

alysis revealed a 1 plus albumin and microscopic hematuria. The nonprotein nitrogen was 30 mg per 100 cc. During the first week in the hospital five blood cultures were obtained, three of which were positive for *Streptococcus viridans*. This organism was tested for its sensitivity to penicillin and was found to be completely inhibited by 0.02 units per cubic centimeter.

**Course**—When the first blood culture was reported to be positive, treatment with penicillin was begun. The subsequent course is set forth in Figure 166. It can be seen that during the 160 days in the hospital the patient received four courses of penicillin, separated from each other by only a few days.

With the first course of treatment, which consisted of the administration of 25,000 units of penicillin intramuscularly every three hours for twenty-one days, the patient showed definite improvement. The blood culture became negative after twenty-four hours, and the temperature returned to normal after seven days.

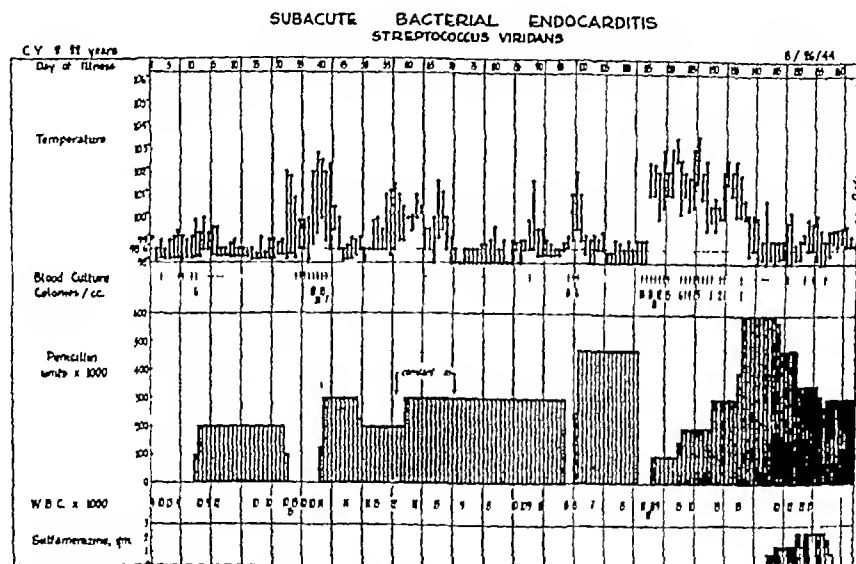


Fig 166 (Case V)—Clinical course of a patient who died of a cerebral embolus after receiving 45,000,000 units of penicillin during the course of 150 days. While the blood culture was never permanently sterilized, this patient's general condition showed very little deterioration during her long stay in the hospital.

Twelve hours after treatment was stopped the temperature rose to 102.4° F, and forty-eight hours later the blood culture again became positive. Treatment with penicillin was thereupon resumed, 25,000 units being given intramuscularly every two hours. When the patient showed signs of improvement, the dosage was reduced after ten days to 25,000 units every three hours. Within three days the temperature again became elevated, and five days later a continuous intramuscular infusion was begun at the rate of 200,000 units a day. At this time the spleen became palpable for a few days. It had not been felt previously and after about a week it could not be felt again.

When the patient failed to improve the daily dosage was increased to 300,000 units a day and was continued at this amount, first by constant intramuscular infusion and later by intermittent intramuscular injections, for thirty-seven days. At the end of this time the patient had been under continuous therapy for fifty-seven days.

Treatment was stopped for three days but was resumed as soon as the temperature began to rise. Three blood cultures taken during the time that treatment was omitted later proved to be positive.

The third course of penicillin consisted of a daily dosage of 500,000 units given in 12 divided doses at two hour intervals for fourteen days. The blood culture again became negative and the temperature returned to normal. During this course of treatment, however, showers of new petechiae appeared almost daily.

As soon as treatment was stopped, the blood culture became positive, although the temperature remained normal for two days. As soon as it rose, treatment was resumed. It was now thought that the patient would probably have to receive penicillin treatment continuously for many months if any hope was to be held for eradicating the infection. Accordingly an effort was made to discover the minimal dosage that would keep the blood culture negative. As can be seen from the chart, the dosage was gradually increased from 50,000 units every twelve hours to 50,000 units every two hours before the blood culture was rendered sterile. After the blood culture had been negative for nine days the dosage was gradually reduced. Sulfamerazine therapy was begun at this time, with the hope that the combined use of the two drugs would permit the use of smaller doses of penicillin. When the dosage of penicillin was reduced however the blood cultures again became positive.

It might be stated at this point that despite the length of the illness the patient's general condition had remained extremely good. Except for the periods when the temperature was markedly elevated, she was comfortable and spent several hours each day sitting up in a chair and walking about the ward. During the latter part of the course, showers of new petechiae appeared almost daily, even at the times when the blood cultures were negative.

After sulfamerazine had been given for seventeen days, the patient complained of increasing nausea and it was decided to discontinue the drug temporarily. Five days later she suddenly complained of an excruciating headache, lapsed into coma, and died one and one-half hours later. An autopsy was not obtained.

This patient received a total of 45,000,000 units of penicillin in the course of 150 days. Despite this prolonged contact with penicillin, however, her organism showed no significant increase in its resistance to penicillin. The organism obtained in the last positive culture was inhibited by 0.04 units of penicillin, whereas the one recovered in the first blood culture was inhibited by 0.02 units. This difference in sensitivity is actually not greater than the range of error of the method of assay used.

In retrospect one may speculate as to whether the use of larger doses earlier in the course of the illness might have controlled the infection as it did in Case IV. Actually the latter patient came under treatment after the patient in Case V had died. This question, of course, cannot be answered. We can say, however, that there are cases on record of patients who have received several million units of penicillin a day over a period of weeks without eradication of the infection. In the light of our present knowledge, however, it seems reasonable to recommend that in those cases that do not respond to more moderate doses the daily amount of penicillin should be gradually increased, if possible, until a daily dosage is discovered that will keep the blood culture

sterile This dosage should then be continued for a minimum of three weeks

Actually, one of the greatest difficulties that the physician encounters in treating subacute bacterial endocarditis is in determining when the patient is making a satisfactory response to treatment Patients who become afebrile and whose blood cultures become negative a day or two after treatment is begun may relapse within a short time after it is completed Other patients whose subsequent course clearly indicates that the infection has been eradicated have not infrequently presented signs during treatment and for several weeks thereafter that strongly suggest an incomplete response to it Thus, experience has shown that fever, leukocytosis, splenomegaly, embolic phenomena, clubbed fingers and an elevated sedimentation rate persisting singly or together after the completion of treatment do not necessarily indicate that treatment has been unsuccessful

The last case that we shall present is an extreme example of this statement

CASE VI—F M., a 29 year old man, was discovered to have mitral stenosis at the age of 7 At 13 and again at 18 years of age he had attacks of acute rheumatic fever After recovering from the last attack, he had no symptoms referable to the heart and remained in good health until the onset of the present illness

Fourteen weeks before admission, without any known precipitating episode, the patient had a shaking chill without localizing signs He remained in bed for four days and then returned to work During the next eight weeks he noticed increasing fatigability and anorexia He continued with his usual activities, however, until five weeks before admission, when he had another shaking chill, followed by a temperature of 103° F The patient then took to bed, where he remained until admission During the intervening five weeks he had a daily afternoon temperature, often as high as 104.6° F, and frequent night sweats He rapidly became very weak and lost approximately 60 pounds in weight Two weeks before admission to the Evans Memorial Hospital he was admitted to a local hospital where a blood culture was found to be positive for *Streptococcus viridans* After treatment with sulfadiazine had effected no improvement the patient was transferred to this hospital

Physical examination showed a pale, emaciated young man, dripping with perspiration, mildly disoriented, and appearing acutely ill There were numerous petechiae in both conjunctival sacs but none in the skin The lungs were normal The heart was markedly enlarged in the region of the left ventricle and the pulmonary conus The rhythm was regular At the apex a crescendo presystolic murmur and a loud blowing systolic murmur were heard The spleen was palpable 2 cm below the left costal margin There was no clubbing of the fingers or toes

Laboratory studies showed the hemoglobin to be 8 gm the red cell count 3,000,000, and white cell count 7000, with 80 per cent polymorphonuclear leukocytes Urinalysis was negative except for a few red blood cells in the centrifuged sediment The nonprotein nitrogen was 40 mg per 100 cc Two blood cultures were positive for *Streptococcus viridans* with 200 and 300 colonies per cubic centimeter The organism was tested for its sensitivity to penicillin and was found to be completely inhibited by 0.04 units per cubic centimeter

**Course**—The hospital course is shown in Figure 167. On the day before treatment with penicillin was begun the patient suddenly complained of a severe headache and lapsed into a state of semicomatose. His neck was found to be markedly stiff and lumbar puncture revealed the spinal fluid to be grossly bloody.

Notwithstanding the patient's poor condition, treatment with penicillin was begun at the rate of 25,000 units intramuscularly every three hours. It was continued at this dosage for seventeen days. For the next four days 200,000 units were administered every twenty four hours by continuous intravenous infusion. Penicillin therapy was then discontinued.

The blood cultures became negative twenty four hours after treatment was begun and remained negative thereafter. The patient, however, showed no significant improvement aside from a slight lowering of the temperature. He remained semicomatose for the first ten days of treatment and was still stuporous and partly aphasic when treatment was completed. When questioned later, he had no recollection of ever having received penicillin.

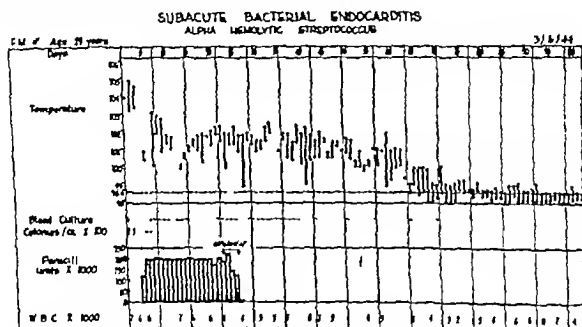


Fig 167 (Case VI)—Clinical course of a patient who despite the persistence of fever splenomegaly embolic phenomena, and an elevated sedimentation rate for several weeks after the completion of treatment, progressed to an apparent complete recovery. Convalescence was extremely prolonged. The patient has now been followed for a period of fifteen months since the completion of treatment and has remained well.

From the chart it can be seen that the patient continued to have fever until seven and one half weeks after treatment was completed. During treatment no new petechiae or embolic episodes occurred, but on the ninth day after stopping treatment embolism of the right brachial artery occurred, and new petechiae appeared almost daily thereafter for the next six weeks.

Seventy five days after treatment was completed an enlarging pulsatile mass that was believed to be a mycotic aneurysm of the right common iliac artery was detected in the right lower quadrant of the abdomen. The aneurysm grew larger for ten days until it was the size of a small orange. Thereafter its size did not change.

It was not until six weeks after treatment was completed that we held any hope for recovery. From that time on, however, the patient showed slow but progressive improvement. Fifty days after treatment he was able to sit up in a chair but another thirty days elapsed before he was able to walk. At that time

he weighed 120 pounds, his normal weight being 175 pounds. Ninety-five days after beginning treatment the patient was discharged from the hospital. The spleen was still palpable at this time and remained so for another three weeks.

During the first three months after discharge from the hospital the patient gained rapidly in strength and his weight returned to normal. At the end of this time there was no longer an anemia and the white cell count and sedimentation rate were normal.

Six months after the completion of treatment the patient returned to work. Another nine months have now elapsed, during which time he has felt entirely well and repeated blood cultures have been negative.

This case demonstrates how difficult it may be at times to evaluate accurately a patient's response to treatment. All that can be said at the moment is that so long as the blood culture remains negative after treatment has been completed, the usual clinical signs that might be taken as evidence of continuing infection must be interpreted with caution. One cannot deny that such signs are disquieting, but the question as to when they should be taken as a signal for the resumption of therapy cannot be answered satisfactorily with our present limited experience. At the moment it is our practice not to give further treatment as long as the blood culture is negative, unless the patient's course as a whole appears to be definitely unfavorable.

#### CRITERIA FOR CURE

The question of what criteria can be established whereby one can be certain that a patient with subacute bacterial endocarditis has recovered from his infection must remain unanswered for the moment. The experience of others has shown that relapses may occur at any time within six to eight months after treatment has been completed, although they are commoner during the first month after treatment than after longer intervals. One case is known in which the patient, after being well for a year, developed anew the typical symptoms of the disease with positive blood cultures. It is of course impossible to say whether this patient actually relapsed or became reinfected.

At the present it is our belief that the prognosis in subacute bacterial endocarditis after treatment with penicillin should remain extremely guarded for the first three months. If the patient remains well during this period, the prognosis improves, but it seems unwise to consider that any patient is cured until at least a year has elapsed from the time treatment was finished. Increasing experience may well necessitate a revision of these figures. Furthermore, the likelihood of reinfection will probably always be present in these patients. With this possibility in mind, it will not be surprising in the years to come to see patients who have recovered from multiple attacks of subacute bacterial endocarditis.

#### PROPHYLAXIS

This discussion would not be complete if we did not close by urging that the prevention of subacute bacterial endocarditis is even more to

be sought than is its cure. The ideal goal in prophylaxis would of course be to prevent the development of rheumatic heart disease and congenital anomalies of the heart and great vessels. Since we do not possess at present the means of accomplishing this goal, we must direct our efforts, in so far as we can, to protecting the patient with rheumatic or congenital heart disease from the incidents or accidents that are known to precipitate subacute bacterial endocarditis.

Even here, our powers are limited. However, much may be accomplished if we can help these patients to avoid all unnecessary surgical operations, particularly those on the oral cavity. To this end early instruction in good dental hygiene is of primary importance. In addition these patients should be thoroughly and repeatedly instructed that should tooth extraction or tonsillectomy become absolutely necessary, they should insist on receiving before and after such procedures a potent chemotherapeutic agent as a prophylactic measure.

A suggested regimen for adults is to administer 2 gm. of sulfadiazine twenty-four hours before operation, and 1 gm. every four hours until forty-eight hours after. The usual precautions that are taken when patients are given a sulfonamide should, of course, be observed. Another regimen is to administer 50,000 or 100,000 units of penicillin intramuscularly no longer than a half hour before the projected operation, and 25,000 units intramuscularly every three hours for twenty-four to forty-eight hours after it. The two regimens may of course be combined.

Prophylactic chemotherapy of this type is now being widely practiced. It is far too early to determine its effectiveness, but until such a time as it is proved to be ineffective, its use appears to be fully justified.

There appear to be two possible mechanisms whereby such prophylactic chemotherapy may exert a beneficial effect. The first consists of a reduction in the number of bacteria at the site of the proposed operation as the result of the preoperative administration of a chemotherapeutic agent, with a resulting decrease in the possibility that organisms will be introduced into the blood stream at operation. By the second possible mechanism, the chemotherapeutic agent would prevent postoperatively the growth and multiplication of any bacteria that might gain access to the blood stream and become implanted on the heart valves. Since sterilization of the mouth is impossible, the second mechanism seems more likely to be operative if prophylactic chemotherapy is effective. It must be admitted, however, that preliminary studies have indicated that preoperative sulfonamide therapy results in a reduction in the incidence of bacteremia following tooth extraction.

Beyond the points outlined above it is not clear how much further one can at present proceed with the prophylaxis of subacute bacterial endocarditis. It has been suggested that all patients known to have valvular heart disease should receive chemotherapy with every res-



piratory infection Should a nontoxic chemotherapeutic agent that can be conveniently taken at home become available, such a program might well be worth adopting

### SUMMARY

In this paper we have reviewed briefly the more important information that is known regarding nonhemolytic streptococcus subacute bacterial endocarditis The treatment of this disease with penicillin has been discussed and illustrative cases have been presented The following points may be repeated in summing up the discussion

1 The infecting organism must be susceptible to penicillin if a favorable response to treatment is to be expected

2 A daily dosage of 200,000 units is the minimal one that has been found to be effective Doses of 300,000 units a day may provide a greater margin of safety Only rarely are larger doses necessary

3 The duration of treatment should be at least two weeks and preferably three weeks In occasional cases more prolonged treatment is necessary

4 Intermittent intramuscular injection at two or three hour intervals is the most convenient and satisfactory method of administering penicillin

5 In 50 per cent of cases the infection responds promptly and apparently permanently to one course of treatment In the other 50 per cent, various complications may be expected These include death from causes not amenable to chemotherapy, failure to respond to the usual doses of penicillin, or the reappearance of symptoms and positive blood cultures either immediately after the completion of treatment or at a later date

6 If the blood culture remains sterile, the persistence of fever, splenomegaly, leukocytosis, embolic phenomena and an elevated sedimentation rate after the completion of treatment does not necessarily mean that therapy has been unsuccessful

7 The formulation of precise criteria for determining when a patient is cured of his infection cannot be made until more experience is available At present it appears advisable to wait until a patient has had negative blood cultures and has been free of symptoms for at least one year before considering him cured

8 Reinfection may occur at any time after the original infection has been eradicated It is not unlikely that multiple attacks of subacute bacterial endocarditis may be observed in the future.

9 The importance of the prophylaxis of subacute bacterial endocarditis has been reemphasized, and the practical measures that the physician can adopt have been outlined

### BIBLIOGRAPHY

- 1 Libman, E. and Friedberg, C. K. Subacute Bacterial Endocarditis New York, Oxford University Press, 1941

2. Smuth C., Sauls, H. C. and Stone, C. F. Subacute Bacterial Endocarditis Due to *Streptococcus Viridans*. A Survey of the Present Status of the Previously Reported Cases and a Clinical Study of 15 Treated Cases Including Another Cure. *J.A.M.A.*, 119:478-482, 1942
3. Dawson, M. H. and Hunter, T. H. The Treatment of Subacute Bacterial Endocarditis with Penicillin, Results in Twenty Cases. *J.A.M.A.*, 127:129-137, 1945
4. Loewe, L. The Combined Use of Penicillin and Heparin in the Treatment of Subacute Bacterial Endocarditis. *Canad. M.A.J.*, 52:1-14, 1945
5. Meads, M., Harris, H. W. and Finland M. The Treatment of Bacterial Endocarditis with Penicillin. *New England J. Med.*, 252:463-474, 1945
6. White, P. D., Mathews, M. W. and Evans, E. Notes on the Treatment of Subacute Bacterial Endocarditis Encountered in 88 Cases at the Massachusetts General Hospital during the Six year Period 1939 to 1944 (Inc.). *Ann. Int. Med.*, 22:61-74, 1945
7. Rosebury T. The Aerobic Nonhemolytic Streptococci. *Medicine*, 23:249-280, 1944
8. Juca, A. and White, P. D. The Cause of Death in Rheumatic Heart Disease in Adults. *J.A.M.A.*, 125:767-769, 1944
9. Grant, R. T., Wood, J. E. and Jones, T. D. Heart Valve Irregularities in Relation to Subacute Bacterial Endocarditis. *Heart*, 14:247-261, 1928
10. O'Neil, C. C. and Elliott, S. D. Bacteremia and Oral Sepsis with Special Reference to Etiology of Subacute Endocarditis. *Lancet*, 2:869-872, 1935
11. Keefer C. S. The Pathogenesis of Bacterial Endocarditis. *Am. Heart J.*, 19:352-363, 1940
12. Christian H. A. Earlier Diagnosis of Subacute *Streptococcus Viridans* Endocarditis. *J.A.M.A.*, 116:1048-1050, 1941
13. Keefer C. S. Subacute Bacterial Endocarditis Active Cases Without Bacteremia. *Ann. Int. Med.*, 11:714-734, 1937
14. Dawson M. H., Hobby G. L. and Lipman, M. O. Penicillin Sensitivity of Strains of Nonhemolytic Streptococci Isolated From Cases of Subacute Bacterial Endocarditis. *Proc. Soc. Exper. Biol. & Med.*, 56:101, 1944
15. Rammelkamp C. H. and Maxon, T. Resistance of *Staphylococcus Aureus* to Action of Penicillin. *Proc. Soc. Exper. Biol. & Med.*, 51:95-97, 1942.
16. Katz, L. N. and Elek, S. R. Combined Heparin and Chemotherapy in Subacute Bacterial Endocarditis. *J.A.M.A.*, 124:149-152, 1944
17. Northrop P. M. and Crowley M. C. Further Studies on the Effect of the Prophylactic Use of Sulfathiazole and Sulfamerazine on Bacteremia Following Extraction of Teeth. *J. Oral Surg.*, 2:134-140, 1944

# THE MANAGEMENT OF CARDIAC EMERGENCIES

CAPTAIN JAMES M FAULKNER

MEDICAL CORPS, UNITED STATES NAVAL RESERVE

THIS discussion will concern itself with the treatment of the following conditions, which may present themselves as acute cardiac emergencies, requiring immediate measures for their relief

## I Cardiac Arrhythmias

### 1 Paroxysmal Tachycardia

#### (a) Auricular

#### (b) Ventricular

### 2 Auricular Flutter

### 3 Auricular Fibrillation

### 4 Adams-Stokes Syndrome

## II Cardiac Tamponade

## III Acute Left-sided Heart Failure

## IV Coronary Occlusion

### CARDIAC ARRHYTHMIAS

**Paroxysmal Auricular Tachycardia**—Paroxysmal auricular tachycardia is characterized by the sudden onset of a very rapid and regular heart rhythm. The rate is usually between 160 and 220 beats per minute, but may be as low as 140 or even lower, and, in infants, is sometimes seen as high as 300. In the absence of heart disease it seldom leads to serious cardiac embarrassment, but in the presence of valvular or coronary disease it may precipitate either congestive failure or severe substernal distress, simulating that seen in coronary thrombosis. Ordinarily it gives rise only to faintness, giddiness, palpitation (often referred to as a fluttering feeling in the chest), and almost invariably to a compulsion to *lie down*. It is apt to be a recurrent condition and patients who have become familiar with it often hit upon tricks of their own which they have found effective in stopping attacks. Favorite devices are holding the breath, taking a long drink of water, and the Valsalva experiment (forced expiration with the glottis closed). I know of one patient who discovered that he could always stop an attack by standing on his head. Most patients agree that these maneuvers are more effective if they are applied at the very beginning of the attack than if they are withheld until the attack has been going on for some time.

The doctor who is called upon to halt a paroxysm of auricular paroxysmal tachycardia should bear in mind that his most effective

---

Nothing in this report is to be construed as official or reflecting the views of the Navy Department or the Naval Service at large

instrument is stimulation of the vagus, that extreme vagal stimulation will almost always stop an attack but at the expense of considerable discomfort to the patient, and that lesser degrees of vagal stimulation will often prove effective and should be tried first.

The simplest and best known maneuver is carotid sinus pressure. This is most effective if the patient is in the upright position or leaning slightly forward. Since stimulation of the right carotid sinus is more apt to be effective than the left, this is chosen first. The patient's head is rotated slightly to the left, the carotid artery is palpated anterior to the sternomastoid muscle and the carotid sinus is identified at the level of the angle of the mandible. The sinus is massaged with strong pressure against the cervical spine. If this is ineffective the same maneuver is carried out on the left, and if necessary both sinuses may be massaged simultaneously. It is well to wait about two minutes between each manipulation because for some reason as yet unexplained it not infrequently happens that the heart rhythm reverts to normal one or two minutes after stimulation has ceased.

The next procedure is to press on the eyeballs. This is less frequently effective than carotid sinus pressure, but sometimes works when the other fails. The amount of pressure applied will be determined by the pain threshold of the patient and the sang-froid of the doctor.

If these measures are unsuccessful, we must resort to more intense vagal stimulation. If the back of the patient's throat is tickled with a tongue depressor or if he sticks his own finger down his throat until he gags, retches or even vomits it will often bring about an immediate cessation of the attack. At this point the physician may well pause and consider whether any more drastic treatment is not likely to cause more discomfort to the patient than the arrhythmia itself. He will remember that these attacks are almost invariably self-limited and unless there is underlying heart disease which makes a continuation of the tachycardia hazardous he should temporize. The patient should be reassured, given a sedative (such as triple bromides 30 grains (2 gm.) or phenobarbital  $1\frac{1}{2}$  grains (0.1 gm.) and put at rest in a quiet room. If, after several hours, the attack has not ceased spontaneously, he may be given syrup of ipecac in repeated doses (10 to 30 cc) until he vomits. This simple but unpleasant procedure will stop most attacks.

As a last resort acetyl-beta-methylcholine ("mecholy") may be given subcutaneously. This powerful vagal stimulant must be used with caution. The patient should be lying down in bed. A sterile syringe containing 1/60 grain (1 mg) of atropine sulfate should be at the bedside to be given subcutaneously or intravenously if an untoward reaction to the drug occurs. A bed pan should also be available in case the drug should cause an evacuation of the bowels. It is best not to use the drug in subjects with asthma as it will invariably provoke an attack in such patients. The dose is 15 to 30 mg in young individuals and 40 to 50 mg in persons over 50. It will cause marked

flushing of the face and body, sweating, lacrimation, palpitation and sometimes defecation. Nausea, vomiting or fainting are signs of clinical toxicity of the drug and call for counter measures. These are the application of a tourniquet above the site of the injection and the administration of atropine either subcutaneously or intravenously. The maximal therapeutic effect of the drug will occur one or two minutes after it is injected at the height of the flush. Its effect on the heart may be enhanced by massaging the site of the injection and by carotid sinus stimulation.

**Paroxysmal Ventricular Tachycardia.**—Unlike paroxysmal auricular tachycardia, paroxysmal ventricular tachycardia is usually associated with heart disease and it is not infrequently an alarming and serious complication of myocardial infarction. It is impossible to differentiate it from the auricular variety with certainty without the electrocardiogram, and treatment for it should never be undertaken without electrocardiographic confirmation. The rhythm is often slightly irregular so that it may give the impression on auscultation of rapid auricular fibrillation. It is not responsive to any of the methods of vagal stimulation outlined above.

As in paroxysmal auricular tachycardia it is well to lead off with a sedative such as triple bromides 30 grains (2 gm), pentobarbital  $1\frac{1}{2}$  grains (0.1 gm) or morphine  $\frac{1}{6}$  grain (10 mg). Quinidine is still the drug of choice in this condition and when given by mouth in the usual doses it is practically without danger, except in the presence of well marked delay in intraventricular conduction and in the very rare case of sensitivity to the drug. With these exceptions it is entirely safe to give quinidine sulfate by mouth in doses of 3 grains every hour up to 30 grains. If this dose is to be exceeded, however, as it not infrequently has to be to bring about the desired result, an electrocardiogram should be taken before each dose in order to stop the drug at the earliest appearance of a toxic effect, which will be a further spreading of the QRS complex. Under carefully controlled conditions 6 grains (0.4 gm) may be given every hour for ten doses with little hazard. If this dosage is ineffective it is better to abandon the oral route with all the uncertainties of assimilation and resort to parenteral administration. Quinidine may be given intravenously but is hazardous in doses above 6 grains (0.4 gm). For parenteral use it is safer to turn to quinine dihydrochloride which is marketed in  $7\frac{1}{2}$  grain (0.5 gm) ampules. It is best given intramuscularly. If given intravenously it must be given very slowly—not faster than  $\frac{3}{4}$  grain every two minutes. Even so it is not without risk and I have seen one death from ventricular fibrillation produced by it. The intramuscular injection which makes for slower absorption is less dangerous.

**Auricular Flutter.**—Auricular flutter resembles auricular paroxysmal tachycardia in that the rhythm is usually rapid and usually regular, but may be distinguished from it in many cases by the fact that the rate is

not so rapid (usually in the neighborhood of 140 beats per minute), and, furthermore, the rate may vary abruptly from time to time. Carotid sinus pressure will usually cause an abrupt but only transitory slowing.

Because the rate is not extremely rapid and because there is a tendency for it to revert to normal rhythm spontaneously it is not necessary to institute immediate measures for its relief unless it persists for several hours or unless the underlying cardiac condition makes it inadvisable to temporize. *Digitalis* is the drug of choice and may have one or more of three effects. It may slow the ventricular rate by increasing the grade of A-V block without breaking up the flutter of the auricles, it may convert the flutter into fibrillation and it may bring about reversion to normal rhythm. It most frequently does all three things in succession. Any of the standard U.S.P. *digitalis* preparations in full digitalizing doses (15 to 22½ grains [1 to 1.5 gm.] of the dried leaf in twenty-four hours), will be found useful but in my experience *lanatocid-C* has been particularly satisfactory when prompt action is desired. It should be given in doses of 0.8 mg intravenously and repeated in four hours if necessary.

**Auricular Fibrillation.**—Auricular fibrillation is much more commonly encountered than auricular flutter. While usually associated with heart disease it is not infrequently observed as a complication of surgical operations or acute infections in older people without other evidence of heart disease and is particularly common in hyperthyroidism. From the point of view of emergency management the features which may call for immediate relief are distressing palpitation and tachycardia. The subjective distress is usually dependent on the tachycardia and patients experience considerable if not complete relief from the palpitation when the rate is brought down to normal limits even though the abnormal rhythm persists. *The immediate objective of treatment is to restore the heart rate to normal rather than to restore normal rhythm* and this is best accomplished by quick digitalization as outlined under the treatment of auricular flutter. Quinidine is not advocated as an emergency treatment in auricular fibrillation but should be reserved for those cases which do not revert to normal rhythm spontaneously following preliminary digitalization.

**Adams-Stokes Syndrome.**—Adams-Stokes syndrome is sudden loss of consciousness due to temporary standstill of the heart. It is seen in high grade partial heart block and in complete heart block and is particularly apt to occur when complete block is not established and there is oscillation between an auricular and a ventricular pacemaker. In the transition from partial to complete block, when auricular impulses no longer reach the ventricle, the ventricular pacemaker may be slow in taking up the rhythm with a resulting excessively long diastolic pause. When such a pause exceeds about eight seconds, sudden loss of consciousness takes place and the aim of therapy is to

stimulate the ventricular pacemaker to a fast enough inherent rhythm so that intervals between beats will never exceed this critical period

The aspect of Adams-Stokes syndrome which the physician is usually called upon to treat, as an emergency measure, is the case in which the patient is having a series of attacks, going in and out of a state of unconsciousness perhaps with convulsions. Under these circumstances the drug of choice is epinephrine (0.5 cc) subcutaneously. This will almost invariably abolish the attacks temporarily (at least for an hour or two) when the dose may be repeated. If a more lasting effect is desired epinephrine in oil (1 cc intramuscularly) may be given two or three times in twenty-four hours. If continued treatment is necessary ephedrine  $\frac{3}{8}$  grain (22 mg) or paredrine  $\frac{1}{2}$  to 1 grain (30 to 60 mg) every four to six hours by mouth may prove adequate.

It is seldom that the physician will be called upon to treat an individual attack since they are necessarily either very brief or fatal, but if he is faced with this problem he must act quickly. The first thing to do is to strike the chest over the cardiac apex sharply with the knuckles several times. This may mechanically stimulate the heart to contract. If this does not bring about resumption of rhythmic contractions epinephrine (0.25 cc of 1:1000 solution) should be immediately injected into the heart. If epinephrine is not at hand the simple thrusting of a needle into the heart may provoke contractions. Needless to say, no time can be taken for sterile precautions. Because these maneuvers are familiar to all of us and because we have seen them carried out with almost invariable lack of success in patients in the death throes of other diseases we should not scorn to use them here, for this is one situation in which they are definitely indicated.

#### CARDIAC TAMPONADE

Cardiac tamponade is the condition in which excessive fluid in the pericardial cavity exerts pressure on the great veins and thus interferes with venous inflow to the heart. It may be caused by inflammatory exudates such as in tuberculosis, pneumococcal or rheumatic pericarditis or by hemorrhage from rupture of an aortic aneurysm of the heart itself. Less commonly metastatic new growth involving the pericardium gives rise to excessive outpouring of fluid into the pericardial cavity. Most dramatic of all are those cases which are due to hemorrhage into the pericardium from stab or bullet wounds of the heart. Since the pericardium is a relatively inelastic membrane, when it is filled with fluid a point is reached where any further increase in its contents causes an encroachment on the caliber of the great veins which enter it. This leads to engorgement of the veins of the neck, enlargement of the liver and a decrease in the stroke volume of the heart which is reflected in a drop in the systolic blood pressure and the pulse pressure.

The immediate therapeutic problem is to lower the intrapericardial

pressure when this has reached a critical point. The best guide as to when to interfere is the pulse pressure. When this falls below 20 mm of mercury the pericardium should be tapped and the fluid removed. This is done with the same technic and apparatus as one would use for a thoracentesis using a short beveled needle to minimize trauma to the heart. The recommended site for tapping is in the fifth left intercostal space about 2 cm inside the left border of percussion dullness. If fluid is not obtained the needle should be reinserted closer to the sternum or in the fourth intercostal space. Another approach is through the epigastrium, the needle being inserted in the angle between the left costal margin and the ensiform and directed upward, inward and to the left in the direction of the left scapula. All removable fluid should be taken away. Immediate improvement in the patient's condition will be noted after the removal of 200 or 300 cc.

In small wounds of the heart, removal of blood from the pericardium by tapping may be all that is necessary. I have seen three such cases—one from a knife wound and two from small shell fragments in which the hemorrhage stopped spontaneously and recovery took place without resort to open operation and suture. Such cases must be watched with greatest care after the first tap to detect signs of recurrence of tamponade which indicate continued bleeding. If signs of pericardial fluid persist but without tamponade it is best to wait and allow it to absorb. If tamponade returns quickly, indicating continued brisk hemorrhage, immediate open operation and suture of the wound should be attempted. If there is a gradual recurrence of the signs of tamponade over a period of hours suggesting a slow oozing of blood into the pericardium, tapping may be again resorted to.

In cardiac tamponade due to hemorrhage, intravenous plasma or whole blood is of particular value because it helps to raise the venous pressure and thus directly to increase the cardiac output. The fact that the venous pressure is already elevated is not a contraindication to raising it still higher by transfusion, because its direct effect is to increase the venous inflow into the heart.

#### ACUTE LEFT SIDED HEART FAILURE

Acute pulmonary edema of cardiac origin results from an overloading of the pulmonary circuit due to failure of the left ventricle to expel as much blood as the right ventricle feeds into the lesser circulation. Because of the limited space allowable for the accommodation of surplus blood in the lungs a discrepancy of only a drop per beat in the output of the two ventricles will inevitably lead in the course of a few hours to extreme engorgement of the pulmonary blood vessels and edema. The most common causes are failing hypertensive hearts, aortic insufficiency or stenosis, infarction of the left ventricle and a tight mitral stenosis. Except in cases of recent infarction the onset of acute pulmonary edema can usually be traced to unusual



exertion, excitement or infection. It is manifested by dyspnea at rest, orthopnea, cough, which may be dry at first but in later stages is productive of white or pink frothy sputum, and cyanosis, which may be marked. The blood pressure is characteristically unchanged or raised. Venous engorgement may or may not be evident.

The object of treatment is to shunt some blood away from the right heart temporarily. This may be accomplished simply by venesection of 300 to 600 cc. If the situation appears to call for quick action only a knife and basin are absolutely required for the blood letting. Relief is usually prompt and dramatic. Often patients who appeared to be at death's door will, within a few minutes, declare they feel as well as ever. Other, less drastic methods are, however, often effective and may be tried while preparations are being made for the venesection if it proves necessary. These are (1) the administration of nitroglycerin grain 1/100 (0.5 mg) under the tongue which has the effect of pooling blood in the splanchnic circuit and thus reducing the return flow of blood to the heart, or (2) the application of tourniquets to all four extremities with a pressure sufficient to prevent venous return flow from these parts. A considerable amount of blood can be excluded from the circulation in this way. The best tourniquet for this purpose is the blood pressure cuff inflated to about 50 mm of mercury. The tourniquets should be left on for about half an hour and released one at a time at intervals of a few minutes. It is a technic which in my experience has been satisfactory in the hospital where plenty of assistance and apparatus is available, but which is sometimes difficult to apply in the home. Whatever the technic used, a hypodermic injection of morphine sulfate  $\frac{1}{4}$  grain (15 mg) should be given at the onset of the attack. This in itself appears to have a specific effect over and above what one would expect from merely alleviating the sense of dread and anxiety which are almost invariably associated with it.

#### CORONARY OCCLUSION

The intimate relationship between angina pectoris and coronary thrombosis is now well recognized and, indeed, there is evidence from postmortem studies of the coronary circulation that angina pectoris is practically always associated with thrombosis of one or both of the main coronary arteries. From the practical point of view it is justifiable to *treat the first attack of angina pectoris as if it indicated a recent coronary thrombosis. The same doctrine applies to any abrupt decrease from the usual amount of exertion required to bring on an attack* (provided extraneous factors such as anemia, infection, hyperthyroidism and exposure to cold are ruled out), *and especially to the onset of angina decubitus.* If we recognize such attacks as danger signals quite different in their significance from the oft-repeated attacks of angina of effort we may, by appropriate measures, lessen the likelihood of myocardial infarction. Acting on the assumption that such attacks may

mean that an actual coronary thrombosis has occurred we should do everything possible to rest the heart until a collateral circulation has had time to establish itself

Once we assume that coronary thrombosis has taken place the immediate objective of treatment is to prevent the onset of myocardial infarction or at least to keep the size of the infarct as small as possible. Infarction results when the local demand for oxygen exceeds the available supply. The aim of treatment therefore is first to reduce the demand for oxygen by complete rest while collateral channels are accommodating themselves to feed the area formerly supplied by the occluded vessel and, second, to increase the local arterial oxygen supply if this be possible.

Objective No 1, complete rest, is obtained by putting the patient to bed at once. The bed should have a moderately high head rest. He should be given morphine  $\frac{1}{4}$  grain (15 mg) at once and this should be repeated if pain continues. This will not only relieve the physical pain but will alleviate to some extent the dreadful anxiety which is so often associated with this condition.

Objective No 2, augmentation of the local oxygen supply to the affected myocardium, is to be attempted by increasing the oxygen content of the arterial blood. This is most effectively accomplished by the administration of 100 per cent oxygen in a closed mask. Even though cyanosis is not evident and the oxygen saturation of the arterial blood is normal the additional oxygen which this makes available both as oxyhemoglobin and in physical solution in the blood may be of critical value in combating the local myocardial anoxia. As an indication of this effect one not infrequently observes complete relief of heart pain on administration of oxygen with recurrence when the oxygen is discontinued. In general, the oxygen should be continued as long as heart pain persists.

Complete rest, morphine and oxygen are the mainstays of immediate treatment in coronary thrombosis. Nitroglycerin is not indicated and may actually be dangerous in cases with impending circulatory collapse. Aminophylline 4 grains (0.25 gm) intravenously may be used as an adjunct for the relief of pain but it cannot take the place of morphine. Papaverine has not yet convincingly demonstrated its usefulness in coronary occlusion as it has in peripheral arterial occlusions and further clinical trial will be necessary to establish its efficacy as a coronary vasodilator in this condition.

A brief outline has been given of emergency measures for the relief of the common acute cardiac disorders. It will be noted that these measures are highly specific and depend upon equally specific accuracy in diagnosis for their successful application.

## THE THERAPEUTIC CONTROL OF RECURRENT PEPTIC ULCER

FRANZ J INGELFINGER, M D \* AND ROBERT E MOSS, M D †

THE patient with an uncomplicated peptic ulcer presents a rather startling therapeutic paradox. His immediate response to medical therapy is excellent, his outlook for the future, by contrast, is dark. The chances are more than fifty-fifty that his ulcer will again trouble him within two years, and the likelihood of a recurrence in five years is probably over 65 per cent<sup>1, 2, 3</sup>. It follows that emphasis today need not be placed on the immediate therapy of the active ulcer, for which several satisfactory regimens have appeared in these pages,<sup>4, 5, 6, 7</sup> but upon the ways and means whereby reactivation of a healed ulcer can be prevented. Recent studies with enterogastrone,<sup>8</sup> a gastro-inhibitory substance extracted from the small intestine, hold out the hope that such substances may eventually be used for the long-term therapy of the ulcer patient. Enterogastrone, however, is still in the experimental stage, and at present one must content himself with more indirect methods of combating ulcer recurrences.

The methods outlined in this clinic are directed against those factors which are generally believed to play a part in the pathogenesis of a peptic ulcer. Both physician and patient may argue that some of the procedures are unnecessary, time-consuming and expensive, particularly since the patient under discussion has a healed ulcer and is free of symptoms. In view of the high incidence of recurrences, however, such arguments cannot bear much weight. In the long run, time and money lost in taking care of a recurrent ulcer—possibly an ulcer complicated by bleeding or obstruction,—greatly exceed the loss incurred by adopting a program aimed at preventing the recurrence. Too vigorous a program, it is true, will be discouraging and will lead to deviations from the too narrow path. The best schedule calls for some effort on the part of the patient, but not for a wholesale abandonment of the pleasures of life.

---

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston.

\*Assistant Professor of Medicine, Boston University School of Medicine, Member of Department, Robert Dawson Evans Memorial, Physician, Medical Service, and Chief, Gastrointestinal Outpatient Clinic, Massachusetts Memorial Hospitals.

†Instructor in Medicine, Boston University School of Medicine, Assistant Physician, Robert Dawson Evans Memorial, Assistant Visiting Physician and Chief, Psychosomatic Medicine Outpatient Clinic, Massachusetts Memorial Hospitals.

How successful is a program of prevention apt to be? Obviously, no guarantee can be given, some ulcers will recur no matter how carefully the patient is handled. On the other hand, we believe that the methods here outlined will, in a large number of ulcer cases, reduce the chances, frequency and severity of recurrences.

#### A SUGGESTED REGIMEN

The patient is assumed to have had a peptic ulcer, now healed and not causing any symptoms. Some parts of the regimen to be prescribed—i.e., those dealing with the patient's education and personality—should actually be started during treatment for the active ulcer.

1 Education.—The basic facts of peptic ulcer should be explained to the patient. By giving him an appreciation of the causes and course of his illness, two objectives will be attained. First, he will not be subject either to the carelessness of ignorance, or to the worry occasioned by various misconceptions that he may harbor. Second, he will follow directions more intelligently and more cooperatively if he understands the purpose of the prescribed regimen. The exact terminology used by the physician in elucidating peptic ulcer naturally depends upon the patient's background, but the following major points can be expressed in language understandable to most laymen.

(a) The exact cause of peptic ulcer is unknown, but physicians do know that an ulcer gets worse when the stomach is overly active and produces more than the usual quantities of acid.

(b) Excess activity and excess acid production by the stomach are particularly apt to occur under the influence of certain mental states and as a result of poor dietary habits. Therefore, the aim of ulcer prevention is adjustment of the mental states and elimination of poor habits. In addition, gastric acidity can be diluted and partially neutralized by the frequent intake of suitable foods and, if needed, medicines.

(c) Individual peptic ulcers can be cured quite readily, but the *tendency* of the patient to get an ulcer cannot be cured. ulcers can and do reappear under the proper conditions. Hence, if the patient is to avoid a recurrence, he must be ready to follow a moderate form of treatment for years.

For purposes of reassurance, the patient is told that duodenal ulcers never become cancerous. Whether he should be warned of complications—i.e., perforation, bleeding and obstruction—is a debatable point. To mention these dangers in a blunt or threatening fashion will serve no purpose but to make the patient unduly apprehensive. On the other hand, he should be informed of the possibility of bleeding so that he may acquire the habit of observing his stools routinely for signs of melena or blood.

2 Psychotherapy.—That peptic ulcer patients present striking similarities in appearance and in personality is generally recognized. Most

therapeutic regimens, consequently, advocate treating the individual as well as the ulcer. How can this be done? Simple admonitions to "take things easily" and to "stop worrying" are not sufficient, the patient obviously would rest and free himself of worry if he could. On the other hand, it is neither necessary nor practical to refer most ulcer patients to a trained psychiatrist. Much can be accomplished by the physician who grasps the essentials of the ulcer patient's personality and who is willing to practice some of the simpler techniques of psychotherapy.

*Description of the Personality*—Freudian psychoanalysis<sup>9</sup> indicates that the ulcer patient has a strong wish to be cared for and loved as he was in infancy. As a result of the early infantile association of being loved with being fed, he desires food as a symbol of security and affection, a desire which maintains the stomach in a constantly active state. Such an attitude is incompatible with the striving of the adult for independence and activity. Hence, the wish to be cared for and fed is repressed into the unconscious, while the conscious mind is occupied in overcompensatory fashion with desires to be the efficient, responsible, conscientious, aggressive leader. As a result, marked conflict is present within the individual and is evidenced by chronic emotional tension.

Approaching the problem on the conscious level by the interview method, Draper and his associates<sup>10</sup> have reached similar conclusions which they express somewhat differently. Ulcer patients, according to these authors, are extremely conscientious victims of chronic fear, who are driven to strive constantly toward some goal regardless of the difficulties encountered. Their driving fear stems from their dimly sensed awareness of the "feminine component" (passive, receptive tendencies) in their make-up which seems to threaten their ability to play successfully the masculine role in life. Thus "basic male fear" presses them to reassure themselves by overemphasizing their virile, aggressive tendencies.

Thus, the male ulcer patient suffers from a deep-seated conflict which is manifested in an excessive load of anxiety—apprehensive anticipation—and concomitant bodily tension. Plainly he must be restlessly active, worrisome and unable to relax. A similar emotional pattern usually characterizes the female ulcer patient, although the underlying conflicts are influenced by the difference in sex.

*Correlation of Gastric Physiology and Personality Reactions*—Suggestive observations of far-reaching importance have been made by Wolf and Wolff<sup>11</sup> on the stomach of their subject, Tom, through whose gastrotomy they were able to study the physiologic changes in gastric function occasioned by varied stimuli. In response to acute aggressive feelings and anxiety, his gastric mucosa became engorged and much redder than usual, the levels of free acid secretion and total volume of gastric juice were three times normal, and there was a

vigorous increase in gastric motor activity. Similar changes of hyperemia, hypersecretion, hyperacidity and hypermotility occurred and persisted during periods of prolonged anxiety and resentment, nor did these effects subside during sleep. Tom's emotional reactions, in short, caused his stomach to assume a state of preparedness for the reception and digestion of food.

Further, in normal subjects and in patients with the clinical diagnosis of peptic ulcer, gastritis and duodenitis, Mittelman and Wolff<sup>12</sup> showed that hypermotility, hypersecretion and hyperacidity occurred in a setting of anxiety and resentment. Such functional disturbances persisted throughout the duration of these emotions and did not abate during sleep. While these changes were present, subjective complaints of pain and epigastric burning were likewise present. The difference between the reactions of the normal subjects and those of the patients was simply a matter of degree.

These observations point toward the local mechanisms for translating emotional reactions into gastroduodenal functional disorders which presumably lead to symptoms and structural changes. They also point the way toward effective management of the patient.

*Psychotherapeutic Method*—Much, then, must be known about the patient in order to understand what influences are affecting his stomach. He should, accordingly, be interviewed privately, in a leisurely, friendly manner that will convey to him the impression that one is interested in him as a person. To encourage him to talk freely about himself, he is asked to describe the onset and course of his symptoms in detail, as these are generally uppermost in his mind. By simple questioning, he can be led to elaborate upon the setting—environmental and subjective, in which symptoms first appeared, persisted or recurred. It is important to ask him how he felt at these times, what he thought about, how he got along with others, how well he was succeeding in his work, and how he viewed his future.

**EXAMPLE 1**—The value of probing closely into the setting in which a symptom first occurs is exemplified by a patient convalescing from a subtotal gastrectomy for obstructing duodenal ulcer. The patient reported that he had begun to vomit as soon as he got home from the hospital and had vomited frequently especially after taking orange juice, during the succeeding three weeks. When asked what the orange juice had reminded him of he recalled that it had upset him repeatedly prior to operation and that he had suddenly thought of this while drinking it. Further inquiry revealed that vomiting had actually begun two days prior to discharge, shortly after he had taken orange juice at breakfast. All the previous night, he remembered, he had felt "jittery" and had slept poorly because he had been given an intravenous injection (a liver function test) the afternoon before. This injection had been given with little explanation; he had immediately concluded that something was still wrong with him and had become acutely anxious. He had thought he could taste the material injected and that it tasted like vomitus. Against this background, the orange juice, which he had been taking daily without distress, precipitated his vomiting. Following discharge, he could not lose the fear that something was amiss, and the gastrointestinal tension was perpetuated, relieved somewhat by periodic vomiting. The elic-

ing of this chain of events opened the way to simple explanation of the purpose of the injection, and to reassurance as to the good result obtained by his operation. Thereafter, the patient ceased to be troubled by vomiting and was able to drink orange juice with impunity.

Usually, an outline of the habitual emotional patterns of the patient during the period of his illness can be obtained at the first interview. This outline suffices for the preliminary formulation of the patient's problem in terms that he can understand. One shows him by summarizing the evidence he has presented that he has an underlying sense of insecurity which is conscious to him as anxiety. This anxiety forces him into a state of constant preparedness for action, manifested by general bodily tension and an inability to relax. The patient usually means these things when he says that he always worries. Experience indicates that any eagerness on the part of the physician to give a more penetrating interpretation early in therapy is unwise. The patient will seldom accept anything more than a rough sketch of the problem, and may well be driven away by an attempt to give him deeper insight quickly.

However, expanding the formulation by pointing out that the patient resembles in his personality make-up a great multitude of peptic ulcer bearers adds to its force and appears to give him a sense of relief by showing him that he has many fellow-sufferers. He is then more easily convinced that his type of personality can lead to overactivity of the stomach. He shows much interest in gaining a clearer picture of the mechanism that produces his symptoms and is, consequently, receptive to instructions aimed at giving him relief.

**EXAMPLE 2**—The beneficial effect upon acute symptoms of the above approach is well exemplified in the case of a 44-year old white man whose ulcer symptoms dated back twenty years. He had been admitted to the hospital because of symptoms indicating severe pyloric obstruction. Constant aspiration of stomach contents for three days, followed by a strict feeding regimen and nightly aspiration, resulted in little relief of pain. The patient was interviewed on the seventh day and the relationship between his anxious, aggressive attitude and his ulcer symptoms was pointed out. He was then given a brief description of the effects of this attitude upon his stomach. The impression this made upon him was striking; he concluded that he could "let go" of much of his anxiety, at least temporarily, and that his aggressiveness was really hurting only himself. Thereafter, his symptoms were greatly alleviated, despite the later finding at operation that the obstruction was largely due to scar tissue.

At the end of the first visit, the procedure to be followed subsequently is outlined to the patient. He will be seen weekly, preferably for one hour at each visit, during which he will be asked to talk in greater detail and with complete frankness about himself. Chronological order is not essential, as significant relationships will come out eventually no matter where he starts. Questions may frequently be necessary, at first, to keep him going, or to bring out further details. As the story of his significant interpersonal relationship unfolds, he is

given a summarizing interpretation at the end of each interview. His appreciation of the reasons behind his early and persisting insecurity will gradually deepen, and he will realize how this feeling of insecurity determined his emotional reactions and, hence, his behavior and health throughout his life.

The development of insight, in this fashion, generally relieves a patient of much of his anxiety with concomitant lessening of his gastric overactivity. The patient, however, must be helped to apply his new knowledge and to understand his reactions in varied situations coming up in his daily living. It is this "working-through" of his problem in as many ramifications as possible that gradually effects a lasting change in attitude which can be summed up as growth in emotional maturity.

In addition, he may be started on a program designed to train him in the art of bodily relaxation. For the intelligent patient a satisfactory recommendation is that he obtain a copy of *You Must Relax* by Jacobson<sup>12</sup> and start putting its principles into practice. Much simplified adaptations of these principles may be presented to the patient who seems unlikely to benefit from reading the book.

The physician, finally, emphasizes that peptic ulceration is the end result of a long chain of circumstances involving the patient's total personality, that successful treatment requires reeducation of his emotional responses as well as a medical regimen, that there is no shortcut to the desired result, and that the length of time necessary to effect readjustments in his personality will be dependent upon his cooperation.

3 Diet—A fairly liberal diet can be offered to the patient with a healed ulcer (Table 1). Much more important than the type of food, however, is *regularity* of eating habits. The patient must eat at the same times every day. This rule has to be stressed particularly to traveling salesmen and others whose work is apt to interfere with regular eating habits. Actually, there are very few occupations which cannot be harmonized with regular food ingestion.

*Interval feedings* of milk must be taken regularly in the middle of the forenoon, in the middle of the afternoon, and at bedtime. If the interval between the evening meal and bedtime is long, an additional glass of milk in the middle of the evening is advisable. Except when asleep, the patient should never go more than three hours without taking food or drink. Milk is without doubt the substance most suitable for interval feedings, but compromises may be made with the patient's taste by using flavoring egg-nogs, custards, junkets, or vegetable purées made with milk. With the milk, plain crackers or cake may be taken if the patient so desires. On the other hand, the patient must understand that other foodstuffs—particularly coffee and soft drinks—are not acceptable substitutes for milk.

Certain foods present particular problems. Caffeine-containing beverages are known to stimulate gastric secretions,<sup>14</sup> hence allowing a



cup of coffee at breakfast (Table 1) may seem questionable. Usually however, an adequate amount of other food taken in the morning will dilute and partially neutralize whatever extra acid is secreted in response to the coffee. The same arguments apply to citrus fruits and their juices. The practice of diluting orange juice half-and-half with

TABLE 1 —DIET FOR THE PATIENT WITH A HEALED PEPTIC ULCER

**Soups** Pureed vegetable soups, preferably diluted with milk. Chicken or meat broths, either clear or with rice. Clam or fish chowder made with milk and potatoes (no onions).

**Meats** As desired, except spiced or pickled meats, very tough meats, or sausages.  
**Fowl** As desired.

**Fish** As desired except spiced, battered or fried fish. Avoid sardines.

**Shellfish** As desired except crab meat.

**Potatoes, Rice, Noodles, Macaroni, Spaghetti** As desired. For sauces, plain tomato sauce made from canned tomato soup and grated cheese may be used.

**Bread** Finely milled bread, whether wheat or rye. Avoid bread containing coal material or seeds of any type. Griddle cakes may be used. Plain crackers made of well-milled flour.

**Vegetables** Avoid raw vegetables. Peas, string beans, squash, asparagus, carrots, beets, spinach, lima beans, tender cauliflower may be used as they are ordinarily cooked. Any other vegetable should be puréed, or strained if it contains seeds.

**Eggs** As desired.

**Cheese** Cream, cottage, muenster, Swiss, mild (white) American. Avoid cheese spreads.

**Butter, Oleomargarine** As desired.

**Sugar, Jelly, Honey, Maple Syrup** As desired.

**Milk, Cream, Cocoa** As desired (flavoring may be added).

**Cereals** Any cooked cereal not containing bran. Corn flakes, puffed rice, wheat flakes, dry oatmeal products.

**Fruit** Apple sauce, ripe banana, baked apple (avoid skin), stewed prunes, canned pears and peaches as desired. Orange, tomato, grape, or prune juice, grapefruit or orange halves, sliced peaches may be used if taken on the full stomach immediately after a meal.

**Coffee or Tea** One cup of either may be allowed with breakfast.

**Desserts** Fruit as above, junket, jello, custard, ice cream, rice or cornstarch puddings (no raisins), fruit whips, gelatine products, plain cakes and cookies (no nuts).

*Avoid the following*

All spices, catsup, mustard, "hot" sauces, relishes, pickles, spicy dressing or stuffing.

Alcohol

Nuts

Carbonated beverages

hot water has little to recommend it, for the only positive effect of this procedure is partial destruction of the heat-labile vitamin C contained in the juice. If the patient experiences heartburn or any other gastrointestinal symptoms after breakfast, it is probably wise to omit both coffee and citrus fruits.

Some patients make a practice of "testing" prohibited foods, to

they eat, let us say, sausage and sauerkraut, experience no ill effects, and understandably reach the conclusion that they need no longer deprive themselves of the pleasures of sausage and sauerkraut. The patient must be cautioned against such "testing." He must realize that when his ulcer is healed, he can probably get away for the moment with eating anything but that repeated ingestion of undesirable foods may contribute to an eventual ulcer recurrence.

*Vitamins* are adequately supplied by the diet. If the patient is unable to tolerate citrus fruits, he requires a daily supplement of 75 mg of ascorbic acid.

*Alcohol* presents a problem in the treatment of ulcer. It is undoubtedly a stimulant of gastric secretion. On the other hand, some feel that its relaxing effects on the mind more than offset its damaging effects in the stomach. It is our belief that relaxation can be achieved more beneficially by other and safer means, and that ulcer patients should entirely abstain from alcoholic drinks.

4 *Smoking*—Over one hundred years ago, Cruveilhier<sup>15</sup> observed that ulcer patients become so irritated at their dietary restrictions, that "there even arrives a period when such stimulants as game succeed much better than white meats." An analogous situation obtains with respect to smoking. Those ulcer patients who can stop smoking without too much effort should certainly do so. But if the attempt to give up smoking leads to an intolerable increase in tension, the denial of tobacco may do the individual's gastrointestinal tract more harm than good. As a compromise, he is allowed to smoke when his stomach is full (i.e., when the presence of food may counteract any noxious effect that smoking may exert), but never when his stomach is empty. This advice runs counter to some very positive statements in the literature,<sup>16</sup> but not all are agreed on the detrimental effects of smoking in the ulcer patient.<sup>17</sup>

5 *Medications*.—Except as indicated under *Preparedness*, no medications are indicated.

6 *Exercise*—Physical exercise, whether during the pursuit of his occupation or at sports, does not harm the patient with a healed ulcer. As is true of all his activities, however, physical *fatigue* or strenuous activity to which the patient is not accustomed are to be avoided.

7 *Follow-up*.—After the emotional problems have been satisfactorily worked out, the patient should be seen once every three months to obtain information not only of his progress, but also concerning his adherence to the prescribed regimen. Often a little reassurance by the physician is helpful in keeping the patient satisfied with and faithful to his treatment. At the time of each check-up a hemoglobin determination and a guaiac test for occult blood in the stools are indicated. Repeated roentgenographic studies are not necessary in following a duodenal ulcer provided symptoms remain in abeyance. On the other hand, it is probably wise to observe the progress of a large duodenal

ulcer by repeating the x-ray studies about one year after the original demonstration of the ulcer

Gastric ulcers present a different follow-up problem because the possibility of neoplasm is ever present, even in gastric ulcers which show complete healing, as judged by disappearance of symptoms and of abnormal roentgenologic findings<sup>18</sup> In such cases, the patient should be seen at monthly intervals for six months, at bimonthly periods for the next half year, and then every three months If symptoms, weight loss or occult bleeding occur, immediate reexamination by roentgenologic means is indicated If the patient remains asymptomatic, repeat x-ray studies should be performed every three months for one year Only by such careful observation can one decide whether one is dealing with a malignant or benign gastric ulceration

8 Preparedness—Some patients notice a seasonal incidence of their ulcer recurrences Others realize that their symptoms are often preceded by certain circumstances colds, emotional upsets, fatigue, and so forth Hence, the patient is advised to adopt a more intensive therapeutic regimen under the following conditions

- (a) At the beginning of a season which, on the basis of past experience, he associates with recurrent ulcer symptoms
- (b) Whenever he is suffering from an acute respiratory infection
- (c) Whenever he is severely fatigued, or when he is performing more than his usual amount of work
- (d) Whenever his emotional tension is heightened, as evidenced by insomnia, restlessness, increased irritability, or "nervousness"

The intensified regimen which is given to ulcer patients under the conditions listed above consists of

- (a) Strict adherence to the interval feedings and diet as given, except that coffee and citrus foods are eliminated completely
- (b) Tincture of Belladonna, 12 minims (0.8 cc) three times a day immediately after meals and at bedtime (Belladonna has been prescribed at various times with respect to meals, we give it immediately after meals in the hope that it may be effective at a time when ulcer symptoms occur one to two hours after food ingestion The optimum dose is one which barely causes a faint dryness of the mouth)
- (c) An antacid, consisting either of

(1) Aluminum hydroxide gel—2 drams (8 cc)

or

(2) A powder—1 dram (4 gm)

Calcium Carbonate 1 part

Magnesium Carbonate 1 part

Bismuth Subcarbonate 2 parts

To be taken one hour *after* meals and at bedtime

- (d) Increased physical rest earlier bedtime, rest on week-ends, cancellation of social activities and work which is not essential

The intensified regimen must be initiated *before* symptoms begin. By this means, circumstances which presumably play a role in precipitating a recurrent ulcer may often be prevented from bringing about their lamentable results. If symptoms arise in spite of all efforts to the contrary, the patient should notify his physician immediately.

TABLE 2—INSTRUCTIONS FOR THE PATIENT WITH A HEALED PEPTIC ULCER

Under certain circumstances, peptic ulcer can recur in persons who are subject to this disorder. You can reduce the chances of such a recurrence, however, by following these simple rules:

I. Stick to your diet. If you wonder whether a certain food is allowable, ask the doctor. Do not "test" foods to determine whether they cause symptoms or not.

II. Drink a glass of milk *regularly* half way between meals and at bedtime. You may take simple crackers with the milk if you so desire.

III. Your ulcer is particularly apt to recur

- 1 In the (physician fills in season of recurrence, if any)
2. When you have colds, sore throats, coughs. If you take medicines for these illnesses, take them with milk.
3. When you are physically fatigued or doing more than your usual amount of work.
4. When you are emotionally upset, or more irritable, sleepless or "nervous" than usual.

IV. Hence, whenever you are exposed to any of the circumstances listed under III, you should automatically take steps to prevent an ulcer recurrence.

1. Be very careful to observe points I and II.

2. Take 2 teaspoonfuls of \_\_\_\_\_ one hour after meals and at bedtime (4 times daily).

3. Take 12 drops of Tincture of Belladonna in a half a glass of water just after meals and at bedtime (4 times daily).

4. Go to bed earlier than usual; you do not necessarily have to sleep but it is important for you to get extra rest in bed. Rest on week ends. Cancel social activities and such work as is non-essential.

5. Observe this intensified form of treatment for at least one week. As a rule, it should be observed as long as the aggravating factors listed under III are present.

V. If you have any ulcer symptoms, notify your doctor immediately.

In addition to the diet, a printed list of instructions (an example is given in Table 2) can be given to the patient with advantage. For his memory of verbal instructions may fade with appalling rapidity.

#### SUMMARY

Although an uncomplicated peptic ulcer responds ~~readily~~ to sound medical treatment, ulcers will recur within five years in well over one half the patients. Therapeutic emphasis should ~~therefore~~ be placed on the prevention of recurrences. At present, no specific ~~medication~~ is available for this purpose. On the other hand, the ~~severity~~ severity of recurrent peptic ulcers can often be reduced by a ~~well~~ intensified regimen which opposes some of the ~~factors~~ ~~causes~~ ~~of~~ ~~recurrence~~.

genesis of peptic ulcer, but which is not too arduous for the patient to observe

The proposed regimen embodies the following points (1) education of the patient, (2) psychotherapy, (3) dietary management with interval feedings, (4) regulation concerning alcohol, tobacco and exercise, (5) follow-up observations and (6) preparedness, so that the patient who is exposed to a circumstance known to aggravate peptic ulcer adopts an intensified therapeutic regimen *before* any symptoms develop

#### BIBLIOGRAPHY

- 1 St. John, F B and Flood, C. A A Study of the Results of Medical Treatment of Duodenal Ulcer *Ann. Surg.*, 110 37, 1939
- 2 Holland, A L and Logan, V W A Brief Report of a Follow-up Research in Peptic Ulcer Covering Twenty Years *Tr Am Therap Soc*, 41 86, 1941
- 3 Heuer, G J The Treatment of Peptic Ulcer Philadelphia, J B Lippincott Co., 1944
- 4 Miller, T G The Medical Treatment of Peptic Ulcer *M CLIN NORTH AMERICA*, 128(2) 403 (March) 1944
- 5 Held, I W Management of the Peptic Ulcer Patient *M CLIN NORTH AMERICA*, 126(3) 654 (May) 1942
- 6 Emery, E S., Jr The Treatment of the Patient With an Uncomplicated Peptic Ulcer *M CLIN NORTH AMERICA*, 128(5) 1164 (Sept.) 1944
- 7 Ingelfinger, F J The Treatment of Gastric and Duodenal Ulcer *M CLIN NORTH AMERICA*, 125(5) 1363 (Sept.) 1941
- 8 Ivy, A C The Prevention of Recurrence of "Peptic" Ulcer An Experimental Study *Gastroenterology*, 3, 443, 1944
- 9 Alexander, F The Influence of Psychologic Factors Upon Gastro-intestinal Disturbances A Symposium I General Principles, Objectives, and Preliminary Results *Psychosom. Quart.*, 3 501, 1934
- 10 Draper, G, Dupertuis, C W and Caughey, J L., Jr Human Constitution In Clinical Medicine New York, Paul B Hoeber, Inc., 1944, pp 206-238
- 11 Wolf, S and Wolff, H G Human Gastric Function An Experimental Study of a Man and His Stomach New York, Oxford Univ Press, 1943
- 12 Mittelman, B and Wolff, H G Emotions and Gastroduodenal Function Experimental Studies On Patients With Gastritis, Duodenitis, and Peptic Ulcer *Psychosom Med.*, 4 5, 1942
- 13 Jacobson, E. You Must Relax New York, Whittlesey House, 1942
- 14 Roth, J A, Ivy, A C and Atkinson, A J Caffeine and "Peptic" Ulcer Relation of Caffeine and Caffeine-Containing Beverages to the Pathogenesis, Diagnosis and Management of "Peptic" Ulcer *J.A.M.A.*, 126-814, 1944
- 15 Cruveilhier, J Anatomie Pathologique du Corps Humain Vol I, Xe Livraison Paris, J B Baillière, 1835
- 16 Ehrenfeld, I and Sturtevant, M The Effect of Tobacco Smoking on Gastric Acidity *Am J M Sc*, 201 81, 1941
- 17 Schnedorf, J G and Ivy, A C The Effect of Tobacco Smoking on the Alimentary Tract *J.A.M.A.*, 112, 898, 1939
- 18 Palmer, W L and Humphreys, E M Gastric Carcinoma Observations on Peptic Ulceration and Healing *Gastroenterology*, 3 257, 1944

## SPECIFIC THERAPY IN ACUTE HEMORRHAGIC NEPHRITIS

ALLAN M. BUTLER, M.D.\* AND GERTRUD C. REYERSBACH, M.D.†

MANY years ago Volhard correctly emphasized that an appreciation of the dangers and therapeutic problem of acute hemorrhagic nephritis depended upon the recognition of the pathological process as consisting in a general as well as a renal vasoconstriction. By quoting him<sup>1</sup> we are not only reminded of the validity of his concepts but also of the length of time they have been at hand. "Thus in the acute stages we are dealing with a functional condition which endangers not only the kidney but also the other organs. In the acute stage it is the danger to the heart which is of first and highest importance. The danger to the brain is second, and to the kidneys only third. The danger that the functional condition in the kidney will lead to lasting and irreparable changes increases with the degree and duration of the general vasoconstriction manifesting itself by hypertension. The hypertension, caused by spastic narrowing of the small peripheral arteries, may set in suddenly even overnight. This means an enormous overload for the heart. Increased work can be accomplished only if the muscle fibers of the heart are stretched more than under normal conditions. A certain degree of dilatation of the heart thus is a necessary condition for increased work, but includes a danger of over-distention.

"The clinical picture of acute diffuse glomerulo nephritis, therefore, may present itself in the form of an acute and most severe insufficiency of the heart with dyspnoea of the highest degree, increase of the venous pressure and swelling of the liver. Almost every case that dies in the acute stage of the disease dies of cardiac insufficiency. Digitalis should be given in every such case.

"The second grave danger consists of cerebral edema, causing the convulsions of the so-called eclamptic uremia. This picture of so-called eclampsia, i.e., convulsive uremia, has nothing to do with true uremia caused by renal insufficiency.

"Convulsive uremia consists of increased intracranial pressure† and the equivalent utterances are headache, vomiting, apathy, somnolence and amaurosis. The higher the blood pressure the greater the danger to the brain.

---

From the Children's Medical Service, Massachusetts General Hospital and Department of Pediatrics, Harvard Medical School, Boston.

\* Associate Professor of Pediatrics, Harvard Medical School. Chief, Children's Medical Service, Massachusetts General Hospital.

† Assistant, Department of Pediatrics, Harvard Medical School. Assistant, Children's Medical Service, Massachusetts General Hospital.

‡ Or cerebral ischemia due to vasoconstriction.

"For the success of the treatment the most important factor is that of time. Every day that a patient walks about without having his condition recognized renders the prognosis darker and diminishes the chances of complete ultimate recovery. It is, therefore, necessary to watch for nephritis after acute tonsillitis and other infections just as we are accustomed to do after scarlet fever. And we have to watch for it, not so much in the acute stage of these infections, as during the first two weeks following the fever."

Even today, Volhard's remarks can hardly be improved upon.

The vasoconstriction usually results in only functional disturbances. The responsibility of the physician is to institute therapy which will so limit the circulatory disturbances as to prevent not only sudden death in the acute phase, but also injury to parenchymal renal tissue resulting in irreversible and progressive kidney disease. In addition he must eradicate any residuum of the streptococcal infection which, as described by Longcope and associates,<sup>2</sup> is the etiologic agent of the acute disease.

The verification of vasoconstriction as the underlying physiological disturbance has been provided by Pickering<sup>3</sup> and Rubin and Rapoport.<sup>4</sup> The frequency of cardiac dilatation, myocardial failure and the efficacy of digitalis has been amply demonstrated.<sup>5, 6</sup> The effectiveness of magnesium sulfate, first introduced by Blackfan and Mills,<sup>7</sup> has been nicely described by Rubin and Rapoport.<sup>8</sup> Winkler, Smith and Hoff<sup>9</sup> have increased the effectiveness of this therapy by defining the relationship between therapeutic effect and the plasma magnesium concentration. Their data indicate that the desired vasomotor effect and fall in blood pressure are not obtained until the plasma magnesium has risen from the normal value of approximately 1.5 milliequivalents per liter to 5 meq per liter. As the concentration approaches 10 meq per liter, the tendon reflexes diminish, whereas respirations are not suppressed until the concentration has risen to between 10 and 15 meq per liter.

The purpose of this paper is to describe briefly (1) a typical case of acute hemorrhagic nephritis together with the therapy used in this clinic, (2) a case of acute hemorrhagic nephritis in which the clearly demonstrable clinical manifestations provide evidence that the abnormal physiologic disturbance is widespread vasoconstriction, and (3) a case demonstrating a progression of the acute functional vasoconstrictive stage to one of irreparable organic changes in the kidney with rapidly progressing renal disease which was arrested by recourse to a therapeutic procedure<sup>10</sup> which, to our knowledge, has not been applied previously to such cases.

#### CASE I. TYPICAL ACUTE HEMORRHAGIC NEPHRITIS, ILLUSTRATING THERAPY

A 3½ year old boy was well until four weeks before admission when he vomited for twenty-four hours. Following this he developed a generalized red flush and a temperature of 103° F for one week. He never complained of a

sore throat. He then appeared well for two weeks. One week before hospitalization the child's face became swollen. He became fretful, vomited off and on and complained of headache and abdominal pain. He voided only small amounts of grossly bloody urine. It was noticed by the parents that the child became "short winded."

On admission to this hospital the patient was found to be a well developed, pale looking child with puffiness about the eyes and moderate generalized edema. The temperature was normal the pulse rate was 120 respirations were 26. He weighed 32½ pounds. The skin was clear. The cervical glands were slightly enlarged. The ears, throat and nose failed to show signs of infection. The pupils reacted to light and accommodation. The fundi were normal. The neck veins were slightly distended. There was very slight dyspnea. The apex impulse of the heart was just outside the mid-clavicular line the heart sounds were of poor quality. The pulmonary second sound was louder than the aortic second sound. A blowing systolic murmur was audible at the apex, which was poorly transmitted to the axilla. The blood pressure was 140/110. The liver was felt three finger breadths below the costal margin and was tender. In spite of these signs of congestive failure, the lungs were normal to percussion and auscultation. Costovertebral tenderness could not be elicited. The extremities were normal except for slight edema the reflexes were in order.

The urine was acid with a specific gravity of 1.010, albumin 2 plus, no sugar, acetone or bile. The centrifuged sediment contained many red blood cells, a few white blood cells and occasional red cell, hyaline and granular casts per high power field. Urine culture showed no growth. The white blood count was 9800 with a normal differential count. The red blood count was 3,300,000 and the photoelectric hemoglobin 6 gm. per 100 cc. The blood nonprotein nitrogen was 34 mg and the serum protein 7.1 gm. per 100 cc.

X ray of the chest revealed a diffuse increased density extending from the hilar shadows into both lung fields consistent with congested blood vessels and pulmonary edema. There was a small amount of fluid in each pleural cavity. The heart was not definitely enlarged. An electrocardiogram was not taken.

A diagnosis of acute hemorrhagic nephritis, congestive failure and hypertension was made and the following treatment was instituted:

- 1 Strict "cardiac" bed rest.
- 2 The diet was limited to 600 to 700 cc of sweetened fruit juice. The fluids are limited because of the oliguria and retention of fluid as evidenced by increase in weight and edema. The carbohydrate is given to minimize the utilization of body tissue for energy requirements and thus minimize renal work by reducing the urinary concentration and excretion of urea. We believe this initial dietary regimen is more logical than the complete fasting and thirsting recommended by Volhard.
- 3 The patient was digitalized with cedilanid, 0.3 mg being given on admission, 0.2 mg three hours later.
- 4 Phenobarbital, 32 mg., was given by mouth, as sedation not only favors relaxation and rest but also may result in a lessening of the hypertension.
- 5 After he was digitalized, the child received intravenously 3 gm of magnesium sulfate in 150 cc of 5 per cent dextrose in water (not in saline), over a period of forty minutes. During the infusion the child was observed for flushing of the face, nausea and diminution in



tendon reflexes and respirations Two 10 cc ampules of calcium gluconate were ready at hand as an antidote to respiratory embarrassment due to the magnesium The blood pressure was taken every five minutes, and was lowered from 150/90 to 130/50 The serum magnesium was at an effective concentration of 6.5 meq/l at the end of the procedure

During the next three days the blood pressure ranged between 120 to 100 systolic and 80 to 60 diastolic The signs of congestive failure had disappeared the morning after admission but the heart remained overactive Digitalization was continued by mouth, 36 mg USP digitalis being given daily\* The child voided well and lost 2 pounds in weight The daily fluid intake was liberalized to 1000 cc All seemed to be going well when on the fourth day the blood pressure rose to 150/100 The child became fretful and complained of abdominal pain The heart was very overactive and the liver edge was palpable 2 cm below the costal margin, but was not tender Sedation with phenobarbital was continued Magnesium sulfate, 3.2 gm in 160 cc of 5 per cent dextrose in water, was given intravenously The blood pressure at the beginning of the infusion was 154/92 and 122/65 at the end The serum magnesium concentration was 5 meq/l directly after the infusion.

The next morning, the blood pressure was again 156/96 Four grams of sulfate were infused between 10 and 11 A.M. with a drop in the blood pressure to 115/64 One hour later, 2.5 gm of magnesium sulfate were given by mouth Two hours later (2.00 P.M.), the serum magnesium was found to be at the therapeutically inadequate concentration of 3.6 meq/l The blood pressure again rose to 150/90 Four cubic centimeters of a 25 per cent solution of magnesium sulfate was given intramuscularly and 2.5 gm were given by mouth at 4 P.M. At 6 P.M. the serum magnesium was only 3.5 meq/l Thus the oral and intramuscular magnesium had not maintained the serum magnesium at an effective level The blood pressure then was 138/84

Thereafter the blood pressure dropped to normal levels with but an occasional rise for a short period The maintenance dose of 36 mg of digitalis was given daily for a period of twelve days, being omitted on the seventh day to avoid a cumulative effect The child lost another 2 pounds in weight Fluids were permitted as desired The diet was gradually liberalized, but protein was limited to 30 gm daily and no extra salt was given Supplemental vitamins A, D, C and B's, and Feosol were provided From the eleventh hospital day on, the child was entirely comfortable At that time the lungs were clear by x-ray An electrocardiogram was within normal limits The white blood count

\*The maintenance dose is roughly one-tenth of the twenty-four hour digitalizing dose, the latter being approximately 33 mg per kg of body weight In the oliguric edematous nephritic, the urinary excretion of the digitalis may be less than normal and hence care must be taken lest such patients be overdigitalized

and temperature remained within normal limits, x-rays of the sinuses failed to show sinusitis and throat cultures on admission were negative. The rigid restriction of activity was relaxed.

After three weeks in the hospital, the urine was clearing satisfactorily and the hemoglobin began to rise. The erythrocyte sedimentation rate stayed around 45 mm./hr. by the Westergren method.<sup>11</sup> Tuberculin 1:1000 was negative and a Hinton test was negative.

At the end of the fourth week the child was placed on a normal diet for age and discharged to a convalescent home where normal activity was gradually resumed and recovery was apparently complete.

## CASE II DRAMATIC MANIFESTATIONS OF A GENERALIZED VASCULAR DISTURBANCE

An 11 year old school boy entered the hospital with a chief complaint of dizziness, disorientation and paralysis.

Eighteen days before admission to the Massachusetts General Hospital the boy complained of a headache. It was noticed that his eyes were puffy and trunk edematous. The urine was dark brown. Two days later the child had a generalized convulsion which started in the left arm and lasted 10 minutes. The boy was admitted to another hospital. The record is of interest because of the initial diagnosis, the repeated lumbar punctures and the lack of specific therapy for the underlying disturbance.

On admission there, the boy was conscious and responded to painful stimuli. Blood pressure was 150/110. The urine contained albumin, red blood cells and casts. The blood nonprotein nitrogen was 65 mg. per 100 cc. Shortly after entry the child had three more convulsions. During the night and through the early morning he continued to convulse, none of the seizures lasted more than one minute except for one which lasted two minutes. The child was irrational and incontinent and developed Cheyne-Stokes respirations. Sodium luminal, 2 grains, and 5 per cent glucose intravenously failed to give relief. A lumbar puncture was done revealing an initial pressure of 210 mm. and a final pressure of 175 mm. of water. The clear spinal fluid revealed 116 white blood cells per cubic millimeter with 63 per cent polymorphonuclears, no red blood cells, 2 plus Pandey and sugar of 103 mg. per cent. The smears showed no organisms. It was the impression of the neurological consultant that the child had a meningitis of undetermined type. He advised sulfadiazine therapy\* and repeated lumbar punctures. The spinal fluid and blood cultures were negative. The child remained semi-comatose for three days, then became rational. He had a paralysis of the left arm for one or two days and then developed a right-sided paralysis. He was aphasic. After eight days the blood pressure had fallen to 112/74; the urine continued as before. The paralysis as well as the aphasia were improving somewhat on the tenth hospital day when the child was taken home by the parents.

During the next six days at home he appeared to improve. The following day he complained of dizziness, became disoriented and on the following day was brought to the Massachusetts General Hospital on the advice of the family physician.

Examination revealed a well developed but poorly nourished boy of eleven. He was in no distress. He knew his name, but not his age or how many brothers and sisters he had. The identification of objects was poor. The child stated that

\* A hazardous therapy in the presence of hematuria and particularly so when this is accompanied by the oliguria so frequently present in the initial phase of acute hemorrhagic nephritis.

he "had forgotten many things" and was apparently aware of his mental defect. The temperature was 99° F. There were no signs of an upper respiratory infection, the pupils were equal and reacted to light and accommodation, and the fundi were normal. The heart was not enlarged, the sounds were of good quality. A soft systolic murmur was present at the pulmonic area. The blood pressure was 95/60. The lungs were clear to percussion and auscultation. The liver was not enlarged. A right flaccid paralysis was present, more pronounced in the arm than in the leg. The deep reflexes were more active on the right.

The white blood count was 11,500 (polymorphonuclear 65 per cent, lymphocytes 23 per cent and monocytes, 12 per cent), the red blood count 4,600,000

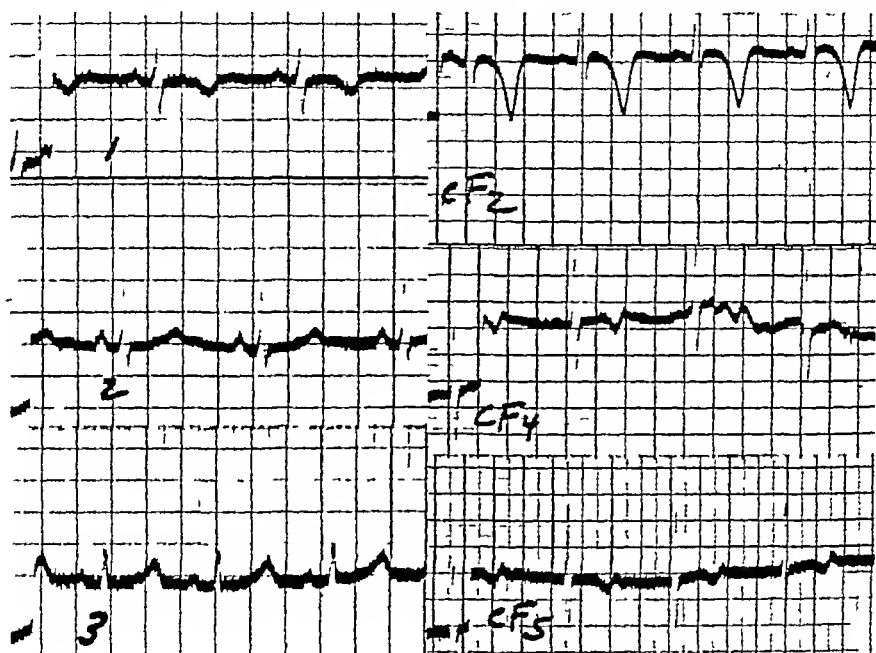


Fig 168 (Case II)—Boy 11 years of age. Electrocardiogram on admission to Massachusetts General Hospital. Rate 75. P-R interval 0.13 sec, normal axis, inverted T<sub>1</sub>, upright T<sub>2</sub> and T<sub>3</sub>, chest leads deeply inverted T in CF<sub>2</sub>, inverted T in CF<sub>4</sub>, diphasic T in CF<sub>6</sub>. The tracing is consistent with the diagnosis of anterior myocardial infarction near the septum.

and the hemoglobin 12 gm per 100 cc. A urine specimen showed a specific gravity of 1.018, albumin 2 plus, no sugar, acetone or bile. The centrifuged sediment contained many red blood cells, 3 to 5 white blood cells and rare red cells and granular casts. The absence of many white blood cells and epithelial cells and the presence of normal concentrations of serum protein, nonprotein nitrogen and cholesterol suggested no extensive damage to parenchymal renal tissue. A normal serum chloride suggested no residual renal damage due to sulfonamide therapy.<sup>12</sup> A Hinton test of the blood was negative and tuberculin 1:1000 was negative.

The heart by x-ray was not definitely enlarged. There was no evidence of pulmonary edema.

A diagnosis of acute hemorrhagic nephritis with cerebral accident due to the hypertension of acute phase was made. In order to deter-

mine any persistence of myocardial involvement, an electrocardiogram was taken which, much to our surprise, showed a tracing which was interpreted by Dr Paul D White to be characteristic of anterior myocardial infarction close to the interventricular septum. Electrocardiograms taken weekly showed gradual healing of the infarction.

As the vascular disturbance of the acute nephritis seemed to have subsided, no specific therapy was given. Under physiotherapy the paralysis improved and the aphasia remained about the same. At the time of discharge, eight weeks after admission, the boy had gained six pounds, the sedimentation rate was normal.

In all probability this patient's convulsions could have been stopped at the time of admission to the first hospital and prevented thereafter, if an appropriate infusion of magnesium sulfate had been given promptly and repeated as indicated. The question as to whether prompt and adequate specific therapy would have prevented the sequelae cannot be answered so assuredly, but certainly the question is worth raising.

### CASE III PROGRESSION IN ABSENCE OF EARLY SPECIFIC THERAPY

Three months before admission D L., a 12 year old boy developed a sore throat followed by bilateral purulent otitis media. At the same time his younger sister had unquestionable scarlet fever. The otitis media was treated with sulfonamides and cleared up. One week later the right ear began to discharge again. The otitis became murky and the mother noticed facial edema. The child complained of abdominal pain. The family physician found a blood pressure of 160/90 and "blood in the urine." The patient was put to bed at home and treated for six weeks with a salt free diet without specific therapy. His urinary output was good but the urine continued to contain albumin, red cells and many casts. On development of a right mastoiditis he was admitted to another hospital.

A summary of that hospital's record showed the following. The admission temperature was 101° F. Red blood count 3.4 million, hemoglobin 70 per cent, white blood count 20,000 with 85 per cent polymorphonuclear cells. The urine contained albumin, red cells and many casts. The nonprotein nitrogen of the blood was 62 mg per 100 cc. Cultures from the ear grew *Staphylococcus aureus*. X rays of the right mastoid region showed increased density and some decalcification but no evidence of cell destruction. Penicillin (12,000 units every three hours intramuscularly) was given as the chemotherapy of choice in the presence of nephritis and hematuria. The temperature and white blood count fell to normal. The mastoid symptoms subsided as did the discharge from the ear. His anemia was improved by a transfusion. However the urine findings remained unchanged and the blood nonprotein nitrogen stayed elevated. The urine volume decreased and he again developed edema of the face and hands. He was then transferred to the Massachusetts General Hospital, eleven weeks after the onset of the hematuria and edema.

Physical examination on admission revealed temperature 99° F; blood pressure 170/104 and weight 73½ pounds. The boy was in no distress. He had minimal generalized edema. The ear drums were normal and he had no signs of an upper respiratory infection. The fundi were negative. The heart was not enlarged. The rate was 70. Murmurs were not heard. The percussion note was flat at the base of both lungs. The liver was palpable just below the costal margin. The remainder of the physical examination was not remarkable.

The red blood count was 5 million, hemoglobin 98 per cent, white blood count 15,000, polymorphonuclears 72 per cent, lymphocytes 24 per cent and monocytes 4 per cent. The urine had a specific gravity of 1.010, albumin 3 plus, no sugar, acetone or bile. The centrifuged sediment contained many red blood cells, 10 to 15 white blood and epithelial cells and numerous granular and hyaline casts per high-power field. The urine culture was negative. Chest x-ray showed the heart was not unusual as to size or shape. There was no definite evidence of pulmonary edema but there was fluid in both pleural cavities. There was haziness of the right mastoid, but no bone destruction. An electrocardiogram was within normal limits. The serum nonprotein nitrogen was 33 mg., protein 5.1 gm., inorganic phosphorus 7.5 mg and cholesterol 357 mg per 100 cc. This diminution of serum protein and elevation of phosphorus and cholesterol together with character of urine sediment were indicative of a progression of the nephritis from an

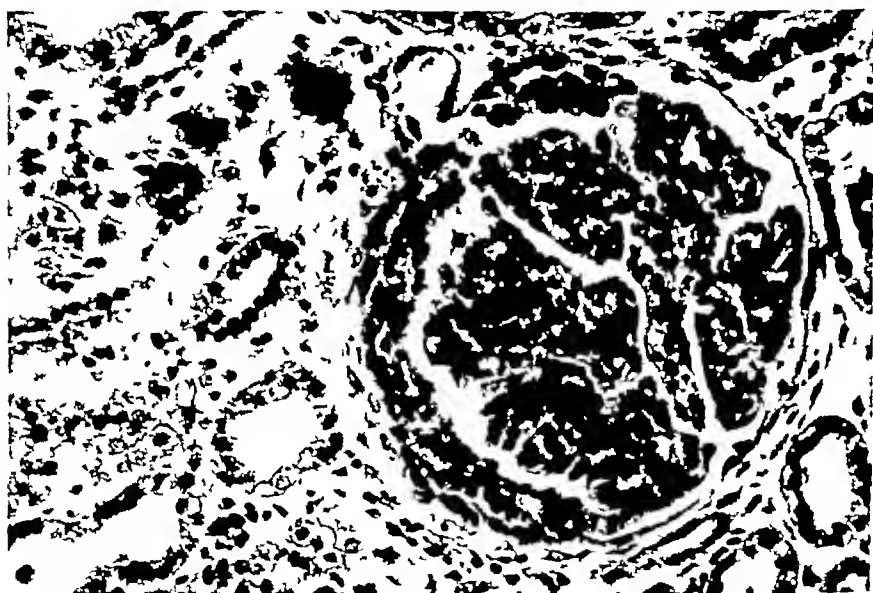


Fig 169—Photomicrograph of renal biopsy (Case III) removed at first operation showing capillary endothelial proliferation and avascularity of a glomerular tuft, and well marked subcapsular extracapillary epithelial proliferation (Courtesy of Dr Benjamin Castleman)

acute reversible stage to a chronic progressive type. A urea clearance test was 15 per cent of normal. Though this might actually have been somewhat greater, as the rate of urinary excretion was low, this degree of reduction of urea clearance eleven weeks after onset of the nephritis confirmed the presence of subacute parenchymal damage.

Intravenous pyelograms showed rather large kidneys in which dye became visible only after one hour.

The patient's temperature remained normal. His urine output was poor and he gained weight steadily. Because of the elevated white blood count and the possibility of residual streptococcal infection, the boy was given sulfanilamide for five days and then penicillin intramuscularly for ten days. As usual when the nephritis has passed beyond

the acute functional stage, the hypertension was lessened only slightly and briefly by magnesium sulfate given intravenously, intramuscularly and orally. The child vomited off and on and complained of dimness of vision. He developed papilledema with retinitis. The blood non-protein nitrogen rose to 41 mg per 100 cc. The serum inorganic phosphorus rose to 8.3 mg with the serum calcium falling to 5.5 mg and the serum protein to 4 gm. per 100 cc.

On the fourteenth hospital day decapsulation of the right kidney was done expeditiously. This procedure, which we hardly ever employ, was resorted to in this case because of the very marked oliguria, the large edematous appearing kidneys by x-ray and the hope that a diminished intrarenal pressure and hence improved volume of urine might follow decapsulation. A renal biopsy was taken at that time. As was consistent with the clinical course, a microscopic section showed a very extensive glomerular nephritis progressing from an acute to a chronic stage (Fig. 169). Following the operation the volume of urine increased somewhat, but the blood pressure remained elevated and the nonprotein nitrogen rose to 51 mg per 100 cc. The patient again developed anemia, the serum protein fell to between 3 and 4 gm per 100 cc. and he had massive edema. Because the prognosis appeared hopeless without interference, it was decided, in consultation with Dr. Reginald Smithwick, to do bilateral sympathectomies.<sup>10</sup>

Left-sided lumbodorsal sympathectomy with decapsulation of the left kidney was performed by Dr. Smithwick on the thirteenth hospital day. Following this the blood pressure remained elevated. Four days after the operation the blood pressure rose to 250/160 and the child suffered a severe hypertensive cerebral crisis with unconsciousness and generalized twitchings. A lumbar puncture done at this time showed a normal spinal fluid with an initial pressure of 140 mm of water. Following the intravenous administration of 6 gm. of magnesium sulfate in 300 cc. of 5 per cent dextrose in distilled water the blood pressure fell to 160/130 and the patient became responsive.

During the next few days the edema increased necessitating an abdominal paracentesis and a thoracentesis. The blood pressure ranged between 240 to 200 systolic and 160 to 140 diastolic. The patient developed mild congestive failure and was digitalized. The calculated dose, 1 gm. of digitalis or 33 mg per kilo body weight, was administered within a period of 36 hours in six divided doses. A maintenance dose of 100 mg was given every other day for a period of two weeks. The edema of the disks and retinitis increased.

The right lumbodorsal sympathectomy was done three weeks after the left. Within two days the blood pressure had leveled off at 150/100. The massive edema persisted. A weight of 93 pounds was 20 pounds above the admission weight. The serum protein remained at 3 gm. per 100 cc. The blood nonprotein nitrogen fell to 36 mg., the serum inorganic phosphorus dropped to 5.3 mg and the serum calcium rose to 7 mg per 100 cc. The urine continued to contain 3 plus albumin, 10 to 15 red blood cells and 5 to 10 white blood cells and many granular casts per high power field. The fundi improved somewhat.

The boy was discharged after a four months hospital stay on a normal diet supplemented with two tablespoonfuls of "amigen." These amino acids were given as readily assimilated protein constituents with the hope of improving the

protein and general nutrition At the same time, because of the danger of nitrogen and phosphorus retention in the plasma, provision was made to follow the serum concentrations of these elements Vitamin D, 2500 IU daily, and one half teaspoonful of B complex three times a day, 15 gm of sodium lactate three times a day and 05 gm ferrous carbonate twice a day were also prescribed

When the boy was re-examined five months later he had lost his edema, was up and about and felt well Blood pressure was 120/80 The urine still contained much albumin The spun sediment showed many white blood cells, a fair number of red blood cells and rare casts The nonprotein nitrogen was 25 mg., serum protein 36 gm., calcium 76 mg and phosphorus 52 mg per 100 cc, the phosphatase was 34 Bodansky units and chloride 109 meq per liter One year later he continues to feel well The serum protein has risen to 58 gm per 100 cc A slight rise in nonprotein nitrogen suggests reducing the nitrogen intake

Here, too, the question may be raised as to whether the prompt institution of therapy to arrest the circulatory disturbance would have prevented irreversible damage to the kidneys The course from completion of the sympathectomy to the present time recommends, in our opinion, future resort to this type of surgical therapy in such cases

#### COMMENT

Perhaps these case histories, by illustrating the physiologic disturbances of acute hemorrhagic nephritis, together with their specific therapy, may provide evidence that patients suffering from this condition deserve more than bed rest, "bland" diet and a too frequently purposeless tonsillectomy Volhard<sup>1</sup> has aptly said "To the practicing physician one of his most important tasks is the treatment of acute diffuse glomerulonephritis It imposes a great responsibility but may also bring the greatest satisfaction"

#### BIBLIOGRAPHY

- 1 Volhard, F The Kidney in Health and Disease in Contributions by Eminent Authorities Philadelphia, Lea & Febiger, 1935, Chap XL, p 689
- 2 Longcope, W T, Bordley, J III and Lukens, F D W *Ibid.*, Chapter XXI, p 330
- 3 Pickering, G W Observations on Mechanism of Arterial Hypertension in Acute Nephritis Clinical Science, 2 363, 1936
- 4 Rubin, M I and Rapoport, M Effects of Magnesium on Vascular Spasm in Rats Arch Int. Med, 59 714, 1937
- 5 Rubin, M I and Rapoport, M Cardiac Complications of Acute Hemorrhagic Nephritis Am J Dis Child, 35 244, 1938
- 6 Whitehill, M R., Longcope, W T and Williams, R Occurrence and Significance of Myocardial Failure in Acute Hemorrhagic Nephritis Johns Hopkins Hosp Bull., 64-83, 1939
- 7 Blackfan, K J and Mills, C A The Effect of a 2 per cent Magnesium Sulphate Solution on the Cerebral Symptoms in Acute Nephritis Trans Am Pediat. Soc., 35 197, 1923
- 8 Rubin, M I and Rapoport, M The Mode of Action of Magnesium Sulphate in Reducing the Hypertension of Acute Glomerulonephritis Am J Med Sci., 201 734, 1941

- 9 Winkler A. W., Smith P. K. and Hoff, H. E. Intravenous Magnesium Sulphate in Treatment of Nephritic Convulsions in Adults. *J Clin. Investigation*, 21 207, 1942
- 10 Smithwick R. H. Surgical Treatment of Hypertension *Arch Surg.*, 49 180 1944
- 11 Rubin, M. I., Rapoport, M. and Waltz, A. D. Comparison of Routine Urinalysis, Addis Count and Blood Sedimentation Rate as Criteria of Activity in Acute Glomerulonephritis *J Pediat.*, 20 32, 1942
- 12 Loetscher J. A., Jr and Blackman, S. S., Jr.. Severe Injury to Kidneys and Brain following Sulfathiazole Administration High Serum Sodium and Chloride Levels and Persistent Cerebral Damage. *Ann Int. Med.*, 18 741 1943



# MANAGEMENT OF THE PATIENT WITH CHRONIC DIFFUSE GLOMERULONEPHRITIS

STANLEY E. BRADLEY, M.D.\*

## GENERAL CONSIDERATIONS

**Pathological Factors**—The unique position of the kidneys in the body economy is responsible for the difficult therapeutic problems of chronic diffuse glomerulonephritis. These organs play a controlling role in cardiovascular dynamics, in the regulation of body water and electrolytes, and in the excretion of the waste products of metabolism. Glomerulonephritis disrupts these functions by interference with glomerular filtration, destruction of tubules, and distortion of the renal vascular bed. Therapy is concerned, primarily, with the correction and alleviation of the pathophysiologic phenomena that result from the structural alterations. No means of halting the disease process is yet at hand. There is general agreement that the course of chronic diffuse glomerulonephritis may be broadly divided into three stages. The first and earliest stage—the *latent stage*—distinguished by minimal and irregular proteinuria, occasional hematuria and a tendency to slight dependent edema or morning facial edema may appear *de novo* or upon the heels of an episode of acute diffuse glomerulonephritis. With further glomerular damage, proteinuria increases and the patient enters the *nephrotic stage* of excessive urinary protein loss, hypoproteinemia, and massive edema formation. Finally, if the process is not arrested by death or reversal, arterial hypertension and renal insufficiency develop in the *terminal stage* of the disease. Although this train of events is commonly seen, in any given instance only one stage may ever be seen or two may occur simultaneously.

**Psychosomatic Factors**—Individuals in whom the disease is discovered accidentally in the course of a casual examination often undergo a rather harrowing experience. In the midst of apparent health, they suddenly find themselves placed apart from other normal persons by their inability to obtain insurance. There are repeated urinalyses, blood chemistry studies, and tests of one type or another. For many people, this sudden diagnostic activity betokens a serious and perhaps fatal illness. Often they even begin to feel unwell and unless reassurance is skillfully practiced, an extraordinary amount of unnecessary mental suffering may result.

---

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts.

\* Instructor in Medicine, Boston University School of Medicine, Assistant Physician, Evans Memorial, Massachusetts Memorial Hospitals.

As a first step in establishing a basis of security, it is necessary to outline for the patient some intelligible account of the disease of which he is a victim, the necessity for the various diagnostic procedures he must undergo, and the objectives of therapy. It is well to remember that prognosis early in the disease may always be optimistic and even in the later stages may be hopeful, since it is known that the process may be arrested spontaneously and permanently, as late in the course as the nephrotic stage, and that even far-advanced renal disease is not inconsistent with several years of life.

In the nephrotic stage of the disease, the huge accumulation of fluid in the tissues may make activity impossible. Alone and immobilized, such patients may become deeply depressed. The radio and occupational therapy are as vital in obtaining good results as efforts to repair the physiological defect at fault. Hope can be offered honestly since it is usual for edema to regress, whether this is a result of further renal damage or of healing.

In the terminal stage, hope should not be denied the patient, but the family should be informed of the hopelessness of the situation. With proper care and good fortune many may live several years. Although protective measures must be taken, it is unfair to forbid all possibly injurious, but enjoyable, activities.

#### MANAGEMENT OF THE LATENT STAGE

It is best to advise the patient in this stage to forget his illness and live a normally quiet life. Dietary restrictions are unnecessary and may even be harmful. Of course, it is unwise for these patients to expose themselves to cold and exhaustion, since acute exacerbation of the renal disease is an ever-present threat. Focal infection should be eradicated under the protection of sulfonamide pretreatment, but indiscriminate tonsillectomy is to be condemned.

Minimal edema may be very annoying. Young women, in particular, complain of this phenomenon because slight edema of the lower extremities quickly produces an unpleasant cosmetic effect and uncomfortably tight shoes. This may be relieved by periods of rest with the feet elevated and a salt-poor diet, together with moderate water restriction.

#### MANAGEMENT OF THE NEPHROTIC STAGE

At this stage of the disease, renal function is usually but slightly impaired. The chief problems are removal of excess body fluid and replacement of the plasma protein. As renal damage increases, many patients imperceptibly enter the terminal stage of outright renal insufficiency and systemic arterial hypertension. Frequently, no clear-cut dividing line is discernible and for a space the two stages overlap. For purposes of clarity the two will be considered as distinctly separate entities in this discussion.

**Plasma Protein Replacement**—Since fluid accumulates in the inter-

stitial spaces as a result of the reduction in plasma proteins, and since albumin makes up the largest portion of the lost protein, the administration of albumin concentrates in sufficient quantity to replace losses seems to be the most logical procedure. Recent experimental work indicates that the proteins of the body are more or less interdependent, comprising a single "pool," the components of which are in equilibrium. Withdrawal of protein from one region (the blood, for example) results in changes of concentration in all areas due to shifts in the reestablishment of equilibria thus disturbed. Consequently, the hypoproteinemia of nephrosis cannot be thought of as a phenomenon limited to the vascular bed, but must be considered part and parcel of a derangement affecting protein stores all over the body. In like fashion, the administration of protein does not result in a contribution of protein to the blood alone but to the total protein pool. The size of this pool, since it includes every area of the body, is enormous and protein concentration in it is not easily affected by doses administered with ease to man. Sachar and his co-workers<sup>10</sup> have shown that the ratio between extravascular and vascular protein in the protein starved dog is of the order of magnitude of 25 to 1. This means that 25 gm of protein must be given to replace 1 gm in the plasma. Probably the ratio is not as large in the nephrotic syndrome in man but even if it is assumed to be 10 to 1, 300 gm of protein must be given to increase the plasma concentration by 1 gm per 100 cc of plasma (assuming a plasma volume of 3000 cc). Obviously, such a dose is impractical. Moreover, albumin concentrates are not yet generally available to the practitioner and only materials in which the protein concentration is relatively low, such as whole blood and plasma, can be used. The fact that immediate and rapid reversal of hypoproteinemia is impossible with the means at hand does not mean that such measures are valueless. At least, urinary protein loss can be compensated for on a gram-for-gram basis in this manner, and diuresis may be stimulated.

**Diet**—For the majority of patients in the nephrotic stage, intravenous replacement of protein is impractical because it is rarely necessary for such patients to be confined to the hospital. For these people, and for bedridden patients as well, dietary measures may prove invaluable. The protein intake must be increased to the point where urinary loss is exceeded. In time, such a diet may result in marked clinical improvement. A sample diet containing 125 gm of protein per day is presented in Table 1. The instructions to the patient should be noted. Salt and water restriction are imperative in the fight against edema formation. Moreover, an attempt to insure appetizing preparation is worth-while, since anorexia may be a serious problem. Adequate vitamin intake is, of course, of great importance. In addition, protein manufacture can be supported and enhanced by intravenous or oral administration of protein digests or amino acid mixtures, such as Amigen and Parenamine.

**Diuresis.**—Although whole blood and plasma transfusions cannot change the plasma protein level significantly, diuresis may be induced by them. The transmembrane protein shifts by which added protein is distributed through the total body protein pool are necessarily slow. During the period of adjustment, the plasma level of protein does rise significantly and even if this elevation is transient, it is of important beneficial influence. The transient elevation of plasma protein increases

TABLE 1 —DIET IN THE NEPHROTIC SYNDROME

## Sample Form

## Diet for M.

It is necessary for you to eat more meat and other protein-containing food because you are losing protein in your urine every day. In addition, your kidneys cannot remove as much water and salt as normal kidneys. Consequently, you must cut down the amount of water and salt you take to avoid water logging your body. The diet below is a sample diet for one day. Substitutes are mentioned. Be sure that your food is cooked without salt and do not use salt at meals.

Breakfast	Fruit	1 serving
	Cereal	(cooked) $\frac{1}{2}$ cup
	Eggs	2
	Bread	1 slice with butter
	Milk	1 glass
	Coffee	As desired with cream and sugar
Luncheon	Meat, fish or poultry	1 extra large serving (4 oz.) may substitute 2 eggs and 1 oz. cheese
	Potato	1 (or other vegetable)
	Vegetable or fruit salad	
	Bread	1 slice with butter
	Milk	1 glass
	Dessert	Choice from list on dinner menu
Dinner	Meat, fish or poultry	1 extra large serving
	Potato	1 (or other vegetable)
	Vegetable	2
	Bread	1 slice with butter
	Milk	1 glass
	Dessert fruit	1 (or sponge cake, angel cake, fruit whip made with egg white, and fruit served with custard sauce, baked custard, or gelatin desserts)

Drink no more than 5 glasses of water each day

the oncotic pressure of the plasma. Water is withdrawn from the interstitial compartment in large amounts, flooding the vascular bed and diluting the constituents of the blood. This dilution brings into operation mechanisms by which excess plasma water is excreted by the kidney, and a diuresis results. If the situation is borderline, this may be sufficient to set in train a series of restitutive processes by which edema is lost. However, in most instances, the protein in the blood slowly falls as a result of loss into the tissue protein pool. The diuresis slackens and finally ceases.

Other diuretic agents, a list of which is given in Table 2, have proved of value in reducing edema. On the whole, these agents act, in one way or another, to increase the osmotic pressure of tubular urine. Urea is probably as effective as any. Some patients object to the taste but, for the most part, it is taken unprotestingly. Mannitol has proved an excellent diuretic in our hands. No toxic effects have been observed and a marked diuresis may be induced. Unfortunately, it must be administered by the intravenous route. Both mannitol and urea appear to be nontoxic under almost any circumstances, but this cannot be said for the other substances listed in Table 2. Potassium salts have found enthusiastic use,<sup>6</sup> but the presence of renal insufficiency makes possible dangerous retention of the toxic potassium ion. Ammonium chloride, too, is popular but this may precipitate a chloride

TABLE 2—DIURETICS

	Dose	Comments
Urea	60 gm per day	Give in divided doses in cold fruit juice
Mannitol	25-50 gm per day	Given intravenously in 25 per cent solution (Sharpe and Dohme) 2-4 divided doses
Potassium chloride	5-10 gm per day	Divided doses. Never use in presence of renal insufficiency
Ammonium chloride	8-12 gm per day	Divided doses. Never use in presence of renal insufficiency or acidosis
Mercupurin	1-2 cc per day	May be given intravenously or intramuscularly. Best response following preparation with ammonium chloride. Never use in renal insufficiency or in presence of diluting impairment

acidosis if caution is not exercised. Finally, mercuripurin and other mercurials have been advocated as extremely effective agents. This is particularly true if the patient has had a course of ammonium chloride therapy. Mercurials appear to induce a chloride diuresis and marked chloride loss may result if an adequate chloride intake is not maintained. A second and greater danger of mercurial medication arises from the potential nephrotoxic action of these drugs.

In certain types of the "nephrotic syndrome" in chronic diffuse glomerulonephritis, impairment of diluting power may be associated with azotemia.

S. H., a 34 year old Chinese, whose course is charted in Figure 170, was such a patient. He was admitted to the Evans Memorial suffering from anasarca, ascites and hydrothorax of four weeks' duration. He presented the classical signs of the nephrotic syndrome, including a marked hypoproteinemia, hypercholesterolemia, and heavy proteinuria. Renal function studies\* revealed a greater re-

\* Mannitol and *p*-aminohippurate were generously supplied to us for these and other studies by Sharpe and Dohme, Inc. For details of clearance procedures see Goldring and Chasis.<sup>5</sup>

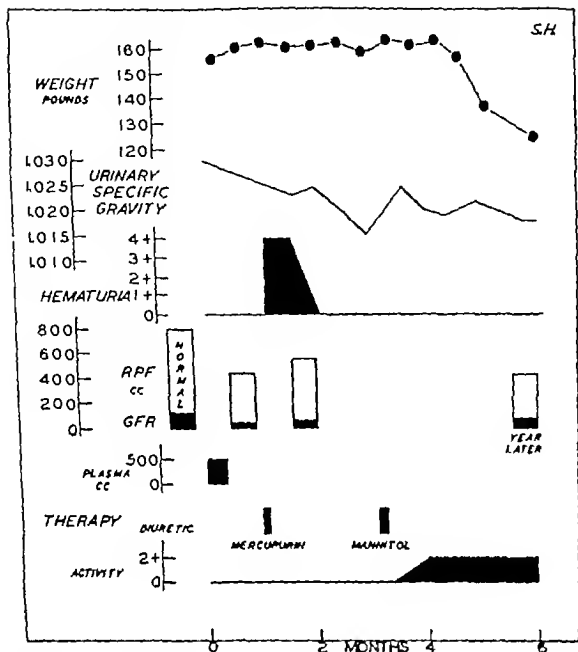


Fig 170—Clinical course and therapy of chronic diffuse glomerulonephritis in the nephrotic stage complicated by azotemia and renal incapacity to secrete dilute urine. S. H., a 34 year old Chinese male, was admitted with anasarca, ascites, and hydrothorax of four weeks duration with no previous history of renal disease. Glomerular filtration rate (G.F.R.—mannitol clearance) was reduced to a greater extent than the renal plasma flow (R.P.F.—*p*-aminohippurate clearance). Nonprotein nitrogen, 74 mg per 100 cc. plasma proteins, 3.64 gm. per 100 cc. cholesterol 353 mg. per 100 cc. and a persistent proteinuria were among the laboratory findings not charted above. Plasma transfusions failed to produce any change in the clinical or laboratory picture. Mercupurin induced gross hematuria and did not provoke diuresis. Mannitol likewise, was ineffectual. A course of thyroid extract (not charted) following mannitol therapy produced no change and was discontinued. A gradual improvement of the clinical picture spontaneously without significant change in blood chemistry permitted reactivation. At present the patient's weight remains at about 130 pounds. Renal function continues to be impaired and other laboratory findings are not significantly altered. Edema rapidly reaccumulates if he deviates from a strict regimen of limited activity, salt and water restriction, and high protein diet. This case demonstrates the danger and ineffectuality of diuretic measures in the nephrotic syndrome in the presence of azotemia and a fixed high urinary specific gravity.

duction in the glomerular filtration rate—GFR (measured by the mannitol clearance)—than in the renal plasma flow—RPF (measured by the *p*-aminohippurate clearance)—a functional pattern<sup>1</sup> consistent with the diagnosis of chronic diffuse glomerulonephritis. In addition, the urinary specific gravity remained persistently elevated and a moderate azotemia was present throughout the course in the hospital.

The patient was placed at bed rest and transfusions of plasma were given daily over a period of ten days without demonstrable change in plasma protein concentration or clinical appearance. Next, mercupurin was administered in the hope of inducing diuresis. Not only did it fail to do this, but definite renal damage resulted in grossly bloody urine. Gross hematuria persisted for a matter of two weeks or more. A third attempt to induce diuresis failed likewise, when mannitol was administered intravenously several weeks later. A course of thyroid extract (0.06 to 0.12 gm. per day) appeared to have little effect. Finally, facial and scrotal edema slowly cleared, without significant weight change, probably as a result of fluid shift to other areas. Then, after approximately four months of bed rest and high protein diet, the edema began to clear, the weight dropping slowly over a two months period to a new constant level, about 40 pounds below the admission weight. During this period he was gradually reactivated without any effect on the process of fluid loss.

On discharge, the patient's lower extremities were still edematous and have remained so to the present. There has been little change in renal function (aside from some improvement in the glomerular filtration rate), urinary protein loss, or plasma protein concentration. The urinary specific gravity over a period of more than one year following onset of the illness has gradually fallen to an average level of 1.015. Azotemia continues to be present.

This case teaches several important lessons. First, diuretic therapy in the presence of a high urinary specific gravity and persistent azotemia is ineffectual and contraindicated. The use of mercupurin in this instance produced further renal damage. The failure of the kidneys to respond to urea, present already in high concentration in the blood, should have been sufficient evidence that other diuretics would be ineffectual. Secondly, the spontaneous regression of edema teaches caution in attributing curative effects to any diuretic or other agents in this disease.

**Risks and Protection**—Inherent in the nephrotic syndrome are the risks of infection of the water-logged tissues and body cavities and of the curious condition known as "the nephrotic crisis." These patients are peculiarly prone to infection by the streptococci and pneumococci. Erysipelas and peritonitis occur frequently and suddenly. Conventional therapy with sulfonamides and penicillin is indicated as well as supportive measures such as transfusion. The presence of glomerulonephritis does not contraindicate the use of the sulfonamides, but they should be used cautiously since additional renal damage is to be feared. In the presence of renal insufficiency, it is likely that the inability of the kidney to excrete concentrated urine prevents a dangerous concentration of sulfonamide in the tubular urine. In the nephrotic stage, particularly in cases like S. H. described above, the danger is greater. Since excretion may be less rapid than normal, dangerously high blood

levels may be attained very rapidly with relatively small doses. Hence, frequent determination of the blood level is necessary. The initial dose of any sulfonamide need differ in no way from that commonly used, but sustaining doses must be reduced greatly, depending upon the blood level obtained. Penicillin, too, may be given in smaller daily doses because excretion is reduced.

The "nephrotic crisis" is characterized by a sudden onset of a sterile or bacterial peritonitis associated with a marked hypoaminoacidemia. Farr<sup>2</sup> and others<sup>3</sup> have shown that the fatality rate can be greatly reduced by intravenous administration of amino acids. Amino acids may be given intravenously as Amigen (Mead Johnson)—one to two liters of 5 per cent solution in 5 per cent glucose daily—or Parenamine (Stearns)—one bottle (100 cc.) in one liter of 5 per cent glucose, one or two times each day. Amino acid mixtures must be given slowly to avoid unpleasant saline reactions of flushing, nausea and vomiting.

Life is restricted, of necessity, for these patients. The rapid appearance of massive edema of the extremities after long standing denies to them occupations in which this is necessary. A sedentary life is forced upon them by the disease rather than by the physician. Nonetheless, a useful and happy life may be assured by careful routinization, by dietary precautions, and by proper use of available therapeutic measures.

#### MANAGEMENT OF THE TERMINAL STAGE

In general, the phenomena manifested in this stage are of either renal or circulatory origin. In many patients a complex of signs arises in part from both types of disorders. In the present discussion, problems that result from hypertension will not be discussed and renal manifestations will be considered as pure states. It cannot be emphasized too strongly that this is a departure from the truth in most instances, since pure states are rare. Simplified formulation of therapy may be misleading if this fact is overlooked.

Each patient must be treated individually in the light of a full knowledge of both the circulation and the kidney, and of the degree to which disorders in each infringe upon and complicate disorders in the other. Complete analysis of the patient's physiological status is necessary. The body water electrolytes can be estimated by determination of plasma carbon dioxide combining power, chloride, calcium and phosphorus, and chemical imbalance calculated roughly from these facts. The state of hydration must be evaluated from clinical signs, from the history, and from the study of the water balance. Occasionally the hematocrit is helpful, but since most of these patients are anemic, interpretation is often difficult. A knowledge of the plasma protein is always helpful. Electrolyte and protein loss may require quantitation of daily loss in the urine, so that adequate replacement may be possible. There are many more complicated procedures by



which a clearer picture may be drawn, but those mentioned are generally available and extremely useful

**Dehydration**—When damage to both glomeruli and tubules becomes very severe the functional balance between the glomerulus and its attached tubule is lost. Many nephrons become permanently diuretic as a result of a glomerular filtration rate beyond the capacity of tubular water reabsorption. The failure of water reabsorption may lead to marked water and electrolyte loss. Most patients respond to the drain by increased water intake, but occasionally the thirst mechanism may be impaired. In these cases, dehydration may develop insidiously. All patients in this stage of the disease should be warned of the increased need for water and increased intake prescribed. Polyuria and nocturia, that prove annoying and even exhausting, develop. If nocturia is so profuse as to interfere markedly with rest, a regimen of water intake designed to produce the greatest output in the waking hours of the day should be laid out. Chloral hydrate (0.5 to 1.0 gm.), phenobarbital (0.03 to 0.06 gm. or 4 cc. of the elixir) and other hypnotics are of value in sedation when they are given during the course of the day or in the evening at bedtime.

When water loss is aggravated by diarrhea and vomiting, dehydration may be profound. Under these circumstances, oral replacement may be impossible or inadequate, and fluid must be given by vein. Table 3 summarizes briefly the important forms in which fluid and electrolytes may be administered parenterally. Gluco-saline (equal parts of isotonic saline and 5 per cent glucose solution) is particularly valuable in combating dehydration in renal insufficiency because there is no need for renal adjustment of electrolyte balance. However, the administration of electrolyte must be adjusted to particular needs in individual cases. Hence, any generalization regarding fluid replacement alone is impossible.

**Electrolyte Imbalances**—When water is lost from the body there is always concomitant loss of electrolyte. The extent and character of electrolyte loss depends upon the site of water loss and many other factors. In the terminal stage of chronic diffuse glomerulonephritis, electrolytes may be retained as well as lost and any conceivable electrolyte pattern may develop.

**Anion Loss**—In one type of the disease, sodium-sparing devices appear to respond more or less normally, despite severe renal damage that otherwise, leads to diuresis and chloride loss. Perhaps, also, chloride reabsorption is impaired. In any case, chloride ion and water are swept out of the body in a persistent diuresis and a syndrome, resembling Addison's disease, results. Pigmentation of the skin, particularly of the face, is not infrequently seen in the terminal stage of glomerulonephritis and may complicate the diagnostic problem. Therapy is necessarily directed at replacement of lost salt and water. Isotonic saline must be given together with additional sodium chloride by

mouth in quantities guided by the amount of water and salt lost each day. Desoxycorticosterone and cortical extracts are of no value.<sup>11</sup>

**Cation Loss and Acidosis**—On the other hand, sodium sparing devices may be badly damaged. The ammonia-forming ability of the tubular cells is lost and the tubule appears to lose its capacity to control urinary pH in such a fashion as to conserve base through the manipulation of urinary buffers. The excess loss of base inevitably leads to

TABLE 3 —INTRAVENOUS FLUID THERAPY IN CHRONIC DIFFUSE GLOMERULONEPHRITIS

	Dose	Comments
1 Sodium chloride 0.85 per cent solution	500-1000 cc. per day	Contains chloride ion in excess of plasma hence if used alone may increase acidosis.
2. Glucose 5 per cent	500-1000 cc. per day	No evidence that it improves renal function in man provides needed food and water, however
3 Gluco-saline (mixture of (1) and (2) equal parts)	500-3000 cc. per day	Fluid of choice for repairing dehydration. Contains chloride in approximately correct proportion, but (4) or (5) must be added to repair sodium defect.
4 Sodium lactate Ringier's solution (1 M)		Add ampule (40 cc.) to 200 cc. of (3) for $\frac{1}{4}$ molar solution—isotonic. Administer 200-300 cc. of 1 M solution diluted properly, and sufficient addition of fluid to correct dehydration as first dose, when $\text{CO}_2$ combining power is less than 30 vol. per cent. Adjust succeeding therapy by effect as shown by clinical and chemical response.
5 Sodium bicarbonate		Ampule (1.5 gm. per 20 cc.) diluted to 100 cc. for intravenous use. Give 15-25 gm. diluted properly, intravenously as initial dose and thereafter according to effect. Oral 10-30 gm. per day.
6 Total volume		Depends on state of circulation and fluid needs. Daily requirements may be estimated grossly by urine flow which should be maintained at 1000 cc. per day. Care should be taken to avoid overhydration.

acidosis if replacement is inadequate. The grave import of acidosis arises not so much from the effects of a lowered pH of the body fluids as it does from the fact that acidosis nearly always bespeaks a serious imbalance of solutes with marked dehydration. The use of the alkalinizing agents listed in Table 3 may be very effective in correcting the chemical and clinical manifestations of acidosis. Nonetheless, treatment must be conducted cautiously. The patients are no longer capable of normal equilibratory responses. The physiological pattern is

brittle and inelastic and overtreatment may be as dangerous as neglect. For this reason, the doses of sodium lactate-Ringer's solution and of sodium bicarbonate are considerably smaller than those conventionally advocated. Proper hydration and careful correction of chemical imbalances must be guided by close observation of the effects. Once they are corrected, the problem of therapy does not end, since the patient's life is one of teetering along a narrow path beset on one hand by acidosis and dehydration and on the other by alkalosis, edema and, perhaps, cardiac decompensation.

The course of H. B., charted in Figure 171, illustrates the effects and hazards of the chemotherapy of acidosis.

This white male of 24 years was admitted to the Evans Memorial complaining of nausea, vomiting, and "shortness of breath" of sudden onset and short duration. He was emaciated, dehydrated and markedly hyperpneic. Investigation revealed fixation of the urinary specific gravity at 1.010, nitrogen retention, and a striking reduction in the carbon dioxide combining power. The blood pressure was slightly elevated, but the cardiovascular system was otherwise normal. There was no history of previous renal disease. Since he was conscious, well-oriented and cooperative, fluids and sodium bicarbonate (12 gm daily) could be given by mouth. Sodium lactate-Ringer's solution (160 cc of one molar solution) was given immediately by vein in 2000 cc of gluco-saline solution. The effect of this regimen was dramatic, both from a clinical and a chemical standpoint. In three days the carbon dioxide combining power had mounted to 26 from 4 volumes per cent. The respiratory pattern reverted to normal and the plasma nonprotein nitrogen fell. Following these changes (due in part, undoubtedly, to hydration) improvement in the chemical pattern of the blood slowed. However, the patient continued to improve clinically and five days after admission he was sitting up in bed, in good spirits, and feeling well. Nonetheless, the carbon dioxide combining power remained at 30 volumes per cent and the nonprotein nitrogen at 63 mg per 100 cc. Continued therapy resulted in moderate pitting edema of the extremities, probably as a result of salt and water retention by the damaged kidneys, and little further change in bicarbonate ion occurred. The dose of sodium bicarbonate was reduced (6 gm daily) and equilibration apparently having been achieved, he was discharged on an alkaline ash diet and sodium bicarbonate. It was thought that the slight edema that remained would act to buffer the tendency to dehydration and acidosis. He remained well on this regimen and returned again to the hospital in acidosis and hypocalcemic tetany only after a lapse from regularity.

The excellent effect of alkalization and hydration is obvious in this case, but the fact that return to the normal state was impossible should be stressed. Therapy must be directed at achieving an optimal clinical response. No single criterion and no perfect clinical pattern can be set up as a satisfactory and safe gauge of therapy. Insistence on one or the other may be fatal. In this case, a vigorous attempt to return the carbon dioxide combining power to normal would have resulted in massive edema.

In addition to the oral replacement of base, dietary restriction of acid ions may be helpful in preventing acidosis. Moreover, the water

which acid ions would otherwise require for excretion is spared to the body. A sample alkaline ash diet is outlined in Table 4

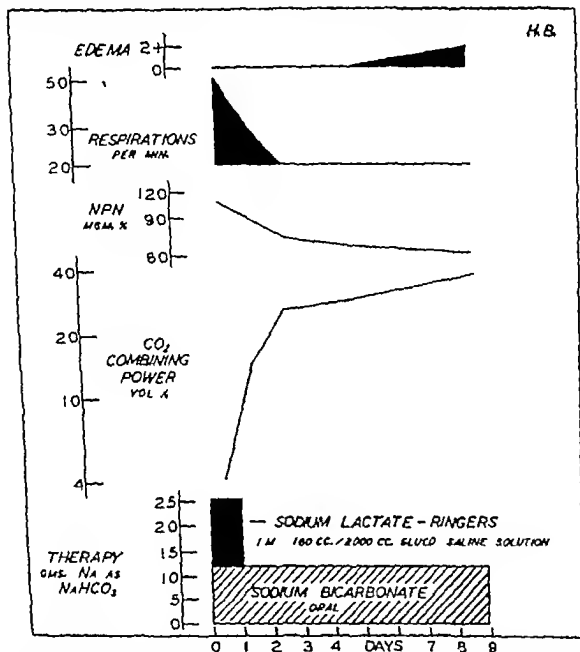


Fig 171.—The treatment of acidosis in the terminal stage of chronic diffuse glomerulonephritis. H. B., a 29 year old white male, was admitted complaining of nausea, vomiting and respiratory difficulty. Renal function was markedly impaired G.F.R., 197 cc. and R.P.F., 1313 cc. The severe acidosis was treated by intravenous fluid and alkalinizing measures on admission. Thereafter water was forced by mouth and sodium bicarbonate was administered. The carbon dioxide combining power rose, but failure of the kidney to regulate the electrolyte pattern and the volume of body water resulted in peripheral edema. This required reduction of the intake of sodium bicarbonate. Discharged markedly improved on an alkaline ash diet and sodium bicarbonate. He remained, however in uremia.

#### Anion Retention

The retention of anions contributes to the development of acidosis in two ways, first, by increasing the concentration of acid ions, and second by stimulating water and base loss. Among the ions retained, chloride and phosphate are the most important. Chloride, in general,

follows the sodium ion, although occasionally preferential retention of this ion does occur. Leutscher and Blackman<sup>7</sup> have reported such an instance following severe renal damage by sulfonamide. This situation may occur in the course of chronic diffuse glomerulonephritis, particularly in severe dehydration. Hydration, preferably with 5 per cent glucose, and alkalinizing measures, if acidosis is present, are indicated.

Phosphate retention leads ultimately to hypocalcemia as a result of the reciprocal relation between the calcium and phosphorus ionic con-

TABLE 4—DIET IN ACIDOSIS

## Sample Form

Diet for M. \_\_\_\_\_

It is necessary for you to avoid acid-forming foods because damaged kidneys are unable to cope with excess acid. Since most meats are highly acid-forming, it will be necessary to replace animal protein with plant protein in your diet. The following diet is a sample diet for one day. Listed below the menu you will find foods you should not eat together with those you may use as substitutes.

Breakfast	Fruit	1 serving
	Toast	1 slice with butter
	Egg	1
	Milk	1 glass
Luncheon	Cheese (cottage)	3 tablespoons, or
	Lean beef	1 medium serving
	Orange	1
	Potatoes	1 (or other vegetable)
	Bread	1 slice with butter
	Baked apple	1 with cream
	Coffee	As desired with cream and sugar
Dinner	Baked lima beans (main dish)	1 serving
	Carrots	1 large serving
	Lettuce	1 large serving
	Bread	1 slice with butter
	Milk or coffee	
	Fruit	1 serving

Drink at least eight glasses of water each day

Avoid Pork, beef, chicken, duck, veal

Eat sparingly of Seafood, lamb, cereals

You may substitute for the above Beans—lima, etc., milk, cheese, eggs

centrations. Calcium is lost in the stool and is precipitated from the blood into soft tissues. Hypocalcemia and acidosis result in a mobilization and loss of calcium from bone and may stimulate the secretion of parathormone. Syndromes resembling rickets and osteomalacia arise from the complex of factors at work. Tetany, muscular twitching and cramps may also appear when hypocalcemia is marked. Difficult and sometimes insoluble therapeutic problems are met.

The bony changes of severe and prolonged renal insufficiency do not respond readily to therapy. The process may be halted by correc-

tion of acidosis and hyperphosphatemia, but, unfortunately, permanent damage and interference with normal growth may occur before a diagnosis is made and therapy instituted. An alkaline ash diet, high calcium intake (e.g., calcium gluconate—4 gm four times a day), and increased vitamin ingestion are usually helpful. Liu and Chu<sup>8</sup> have found that dihydrotachysterol (AT 10)—3 cc daily by mouth—may exert a favorable influence. It is a matter of general experience that vitamin D is valueless in improving calcium absorption in these cases. Often it is impossible to reverse the acidosis completely and one must be satisfied with retarding the pathological process.

Since hyperphosphatemia is a common denominator in all these conditions, it seems reasonable to suppose that increasing the phosphorus excretion would be of value. That this is so is illustrated by the response of H. B. (Fig. 172) to treatment with aluminum hydroxide. This substance (Amphojel—20 cc daily, Creamalin—12 tablets daily) precipitates phosphates as insoluble salts in the intestine.<sup>4</sup> Since phosphate passes from the blood into the gut in the intestinal secretions, augmented excretion by this route results and ultimately a reduction in the blood level with a reciprocal increase in the calcium level occurs. Iron salts (e.g., Feosol—1 gm. four times a day) also have this action.<sup>8</sup>

H. B. was admitted several months after the admission described above. He confessed to dietary indiscretions and he had failed to continue his medication. He was complaining of "shaking" muscular cramps and diarrhea. Evidence of tetany was demonstrable in positive Chvostek and Trousseau signs and in fibrillary muscular twitching. It was noted that the peripheral arteries were calcified. Chemical studies (Fig. 172) revealed hypocalcemia and hyperphosphatemia in addition to a depressed carbon dioxide combining power and azotemia. He was placed on sodium bicarbonate and increased water intake by mouth. There was little change during the following four days. Amphojel was then substituted for the sodium bicarbonate. After three days the plasma phosphate had fallen from 6.2 mg to 4.25 mg per 100 cc. Cessation of the aluminum hydroxide therapy was followed by a rise of phosphorus to a level however considerably below the admission concentration. From this point improvement was progressive, the calcium concentration increasing with alleviation of the symptoms of tetany. The carbon dioxide combining power and nonprotein nitrogen content both changed toward normal levels.

Although in this instance, Amphojel was instrumental in correcting to some extent, a hyperphosphatemia the effects of concomitant measures must not be overlooked. Certainly the reestablishment of a more nearly normal water balance and of other electrolyte concentrations all played interdependent roles in producing satisfactory effects.

**Cation Retention.**—The retention of cations is unusual. However, increased intake may be associated with retention, as in the case of sodium in H. B. noted above. The kidney is fixed in its function to a narrow range of activity and any change from the normal cannot be adequately compensated. Rarely in far advanced renal failure potas-

sium may accumulate to the point of toxicity<sup>9</sup> Reduction of intake, insulin and calcium therapy may be of value here

**Anemia**—A hemorrhagic diathesis often becomes apparent during the stage of renal insufficiency, the cause of which is obscure There

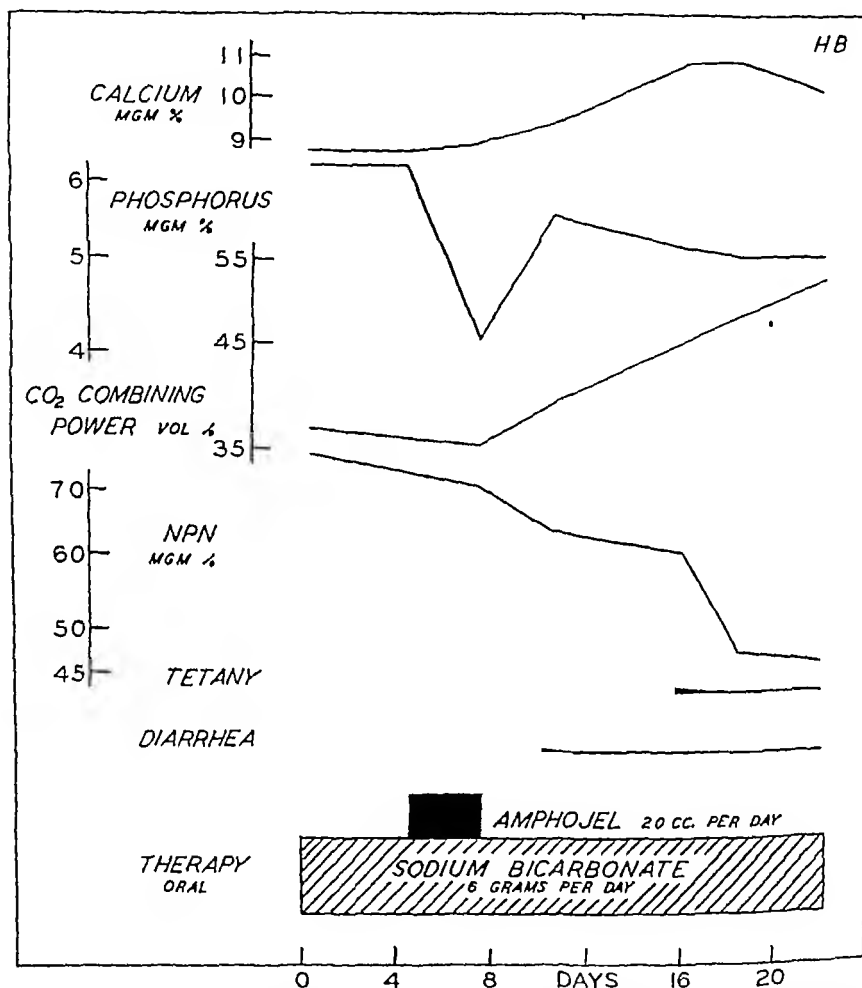


Fig 172—Therapeutic correction of hyperphosphatemia and hypocalcemia in the terminal stage of chronic diffuse glomerulonephritis H B., readmitted complaining of diarrhea and "shaking" Signs of tetany were demonstrated A course of aluminum hydroxide (Amphojel) resulted in marked reduction of plasma phosphate and was followed by gradual restitution of plasma calcium to a normal level Other measures employed in this case included restoration of lost fluid and base

may be bleeding from any mucosal surface—the mouth, stomach, gut, rectum, or the genitourinary tract Thus, blood loss may be a cause of severe secondary anemia, but, as a rule, such an anemia develops at this stage of chronic diffuse glomerulonephritis, and often earlier, for un-

known reasons. It is very difficult to treat, responding poorly or not at all to iron therapy. Repeated transfusions are often the only means by which one can produce even temporary relief.

### CONCLUSIONS

These remarks express, for the most part, tentative opinions. The physiological changes in the course of chronic diffuse glomerulonephritis are not fully explored and understood. Therapy is often ineffective and one must often fall back upon empiricism. Unfortunately, empiricism is doubly dangerous because the variability of the course may give virtue to procedures that do not deserve it, and because meddling interference with a system so intricate as the complex of mechanisms that regulate the composition and volume of the body water must be dangerous. Therapy is therefore to be conducted as cautiously and as understandingly as possible.

1. Earle, D. P., Jr., Taggart, J. V. and Shannon, J. A. Glomerulonephritis. A Survey of the Functional Organization of the Kidney in Various Stages of Diffuse Glomerulonephritis. *J. Clin. Investigation*, 23:119, 1944.
2. Emerson, K., Jr. and Van Slyke, D. D. Nephrotic Crisis. *J. Mt. Sinai Hosp.*, 8:495, 1942.
3. Farr, L. E. and MacFayden, D. A. Hypoalbuminemia in Children with Nephrotic Crisis. *Am. J. Dis. Child.*, 59:782, 1940.
4. Fauley, G. B., Freeman, S., Ivy, A. C., Atkinson, A. J. and Wigodsky, H. S. Aluminum Hydroxide in the Therapy of Peptic Ulcer. Effect of Aluminum Hydroxide on Phosphate Reabsorption. *Arch. Int. Med.*, 67:563, 1941.
5. Goldring, W. and Chasis, H. Hypertension and Hypertensive Disease. The Commonwealth Fund, New York, 1944.
6. Keith, N. M. and Binger, M. W. Diuretic Action of Potassium Salts. *J.A.M.A.*, 105:1584, 1935.
7. Leutscher, J. A. and Blackman, S. S., Jr. Severe Injury to Kidneys and Brain Following Sulfathiazole Administration. High Serum Sodium and Chloride Levels and Persistent Cerebral Damage. *Ann. Int. Med.*, 15:741, 1943.
8. Liu, S. H. and Chu, H. L. Studies of Calcium and Phosphorus Metabolism with Special Reference to Pathogenesis and Effects of Dihydroxycholesterol (A.T. 10) and Iron. *Medicine*, 22:103, 1943.
9. Marchand, J. F. and Finch, C. A. Fatal Spontaneous Potassium Intoxication in Patients with Uremia. *Arch. Int. Med.*, 73:384, 1944.
10. Sachar, L. A., Horvitz, A. and Elman, R. Studies on Hypoalbuminemia Produced by Protein-Deficient Diets. I. Hypoalbuminemia as a Quantitative Measure of Tissue Protein Depletion. *J. Exper. Med.*, 75:453, 1942.
11. Thorn, G. W., Koepf, G. F. and Clinton, M., Jr. Renal Failure Simulating Adrenocortical Insufficiency. *New England J. Med.*, 231:76, 1944.



# THE MANAGEMENT OF SOME COMMON DISTURBANCES OF THE FEMALE BLADDER FUNCTION

SAMUEL N VOSE, M D , F A C S \*

A CONSIDERABLE proportion of the women coming under the care of the urologist do so because of a disturbance of the bladder function with frequency of urination, nocturia, painful voiding, tenesmus and/or various degrees of urinary incontinence as the outstanding symptoms. Often associated with these symptoms is pain in the suprapubic area and the groins or in the lower abdominal quadrants. The frequency with which these cases appear and the usual long history of the complaint with the story of a variety of treatments at the hands of several doctors indicate that this group of cases offers a definite problem to the general practitioner as well as to the urologist. Although in numerous cases these symptoms indicate the presence of *some serious surgical* condition and demand thorough urological investigation in order to establish a diagnosis and indicate treatment, in the majority of instances they are due to local conditions in the bladder or urethra which cause pain and suffering out of all proportion to the seriousness of the pathologic involvement and are amenable to comparatively simple methods of diagnosis and treatment available to any practitioner.

Among the conditions most commonly seen as causes for this group of symptoms and which will be taken up in some detail are

- 1 Acute uncomplicated nonspecific bladder infections
- 2 Interstitial cystitis (Hunner ulcer)
- 3 Chronic nonsuppurative urethritis and trigonitis
- 4 Fibrous bladder neck obstruction
- 5 Gynecologic conditions

With the exception of the first named, all these conditions in their original state are characterized by a *clear urine*, a fact which is of great value in differentiating this group from other more serious diseases which may present the same initial symptoms. This differentiation will be helped, also, by the observance of a few fundamental urologic principles of extreme importance.

## IMPORTANT UROLOGIC PRINCIPLES

- 1 The presence of blood in the urine demands immediate and thorough urological investigation
- 2 Resistant, chronic or recurrent urinary infections usually indicate the presence of some complicating lesion, often obstructive, which

---

\* Professor of Genitourinary Surgery, Boston University School of Medicine, Surgeon-in-Chief, Genitourinary Department, Massachusetts Memorial Hospitals, Boston

must be removed in order to produce a cure. Chronic cystitis is usually a symptom and not a disease

3 The failure of simple treatment to bring about a cure of any of the conditions to be discussed indicates an error in diagnosis or complications that require further diagnostic measures

With these principles in mind and without recourse to extensive urologic procedures, the general practitioner may safely diagnose and treat the majority of these cases

#### OUTLINE OF INVESTIGATION

The *history* is of great importance. Precise information should be obtained as to the frequency of urination, nocturia, the relation of the discomfort to the act of micturition, whether before, during or at the end, the amount passed at each urination, circumstances which aggravate the symptoms, pain in other parts of the body which may accompany voiding, dysuria, and urging or incontinence. The circumstances under which the initial symptoms occurred may be of significance. The patient's theory as to the cause is often of interest and may be of value in diagnosis. The *general history* should pay particular attention to age, menstrual history, antecedent infections, urinary or otherwise, marital status, childbirth, or other trauma, chronic fatigue, and any symptoms suggesting endocrine disturbances. A *general physical examination* is, of course, essential to any diagnosis

**Special Examination of the Genitourinary Organs.**—Thus should include the following in most cases

- 1 Palpation of the kidneys and ureteral areas
- 2 Inspection of external genitalia.
- 3 Bimanual pelvic examination and inspection of cervix by speculum.
- 4 Obtaining catheterized specimen of urine for microscopic examination and culture
- 5 Overdistention of the bladder to reproduce pain of interstitial cystitis.
- 6 Calibration of the urethra

The local examination is best carried out shortly after the patient has voided. There is always sufficient urine left in the bladder to obtain a specimen for culture and microscopic examination, and the passage of the catheter after voiding will reveal the presence of a significant residuum. On inspection of the external genitalia, one notes the condition of the perineum, the presence of a cystocele or rectocele, evidence of infection in Skene's glands, the state of the urethral meatus, particularly as to caruncle, and, in cases of incontinence, one should search for an ectopic ureteral orifice or vesicovaginal fistula. The urethra and base of the bladder are palpated vaginally with particular attention to tenderness and thickening. A soft rubber catheter is passed after thorough cleansing of the vulva with soap and water

A culture should be made from urine obtained at the *first catheterization*, otherwise contamination must be considered as a probability. The specimen is examined chemically and microscopically. Following this, if the urine is *clear and free from pus or blood* 1 ounce of 1 per cent novocaine should be instilled into the bladder and allowed to remain five minutes. It is then withdrawn through a catheter and the bladder is distended to the point of tolerance with sterile water or boric solution, noting character and location of pain caused by overdistention. The fluid is then allowed to run out and the last few cubic centimeters are watched carefully for traces of blood. Such bleeding is highly suggestive of interstitial cystitis, and if the history points to this condition and no blood appears on the first overdistention, the maneuver should be repeated.

The urethra may be calibrated by a metal sound or bulbous bougie. The normal female urethra will easily admit a 26 F sound with little discomfort. A small caliber usually indicates a granular urethritis or stricture.

*If the catheterized specimen contains pus, the above instrumental manipulations should be omitted* and the infection treated as later outlined.

Completion of such an examination will furnish the data essential to a working diagnosis. Details of the diagnostic points will be included in the discussion of the several conditions to be considered.

#### ACUTE CYSTITIS

Infection of the female bladder is extremely common. While this condition is often an acute flare-up of a chronic process in other parts of the urinary tract, such as pyelonephritis, a goodly number of cases are uncomplicated, acute conditions which are usually self-limited, but which respond more rapidly if proper treatment is administered early.

**Etiology**—The shortness of the female urethra is a factor in the frequency of this condition, infection ascending from the vestibule in the wake of trauma of some sort such as that resulting from holding the urine too long after the desire to void occurs. "Honeymoon cystitis" if of similar etiology, as are certain cases of postoperative cystitis. Exposure to cold, chronic fatigue or irritating food or drinks may predispose to such infections. Many cases follow acute upper respiratory infections, and immobilization in bed for minor ills such as fracture of the ankle is often accompanied by cystitis. By far the most common organism is some strain of *Bacillus coli*. *Streptococci* and *staphylococci* are frequently found and particularly resistant infections may result from *Streptococcus faecalis* and *Bacillus proteus*. Infections caused by the last named are practically always due to organisms introduced by instrumentation. Since the choice of a therapeutic agent may be influenced to a considerable extent by the staining qualities of

the infecting organism, its identification by smear or culture as early as possible is desirable.

**Diagnosis**—The symptoms of acute cystitis are quite distinctive, well known and easily recognized. The sudden onset of frequency of urination, urging and tenesmus, with pain on voiding, points unmistakably to a bladder infection. The question is whether the infection is a simple, uncomplicated process or whether it is a manifestation of or accompanied by other more serious conditions. Often this cannot be decided early. A history of previous similar attacks suggests the presence of complications or latent upper urinary tract infection.

**Bleeding** is a common occurrence in acute cystitis. It usually follows by a few hours the onset of other symptoms and is comparatively small in amounts and of short duration, although clots may be present. It is apt to be terminal in character although the female patient is often unaware of this. Dull pain in the loin due to edema of the bladder mucosa may be present, although it usually is not as severe as that of acute pyelonephritis or ureteral obstruction. Constitutional symptoms are mild the temperature rarely exceeding  $100^{\circ}\text{F}$ , and chills are practically never seen. A dull headache and slight malaise are often present.

On physical examination there is rarely any loin or costovertebral tenderness but tenderness in the suprapubic area and soreness in the bladder on bimanual pelvic examination may be found. The catheterized specimen shows varying amounts of pus, and blood cells if the infection is of the hemorrhagic type. The urine should be tested carefully for sugar, as diabetes is an important predisposing factor in many urinary infections. The red or white blood count rarely shows any change due to the infection, but may reveal conditions important in its etiology.

Certain cases of acute gonorrheal infection of the urethra may be mistaken for acute nonspecific cystitis, particularly if the history of exposure is withheld. In this condition pain on voiding is the outstanding symptom, rather than frequency, and the presence of discharge and redness of the urethral meatus should lead to the taking of a smear and culture which will determine the diagnosis.

**Treatment of Bladder Infection**—The treatment of acute cystitis consists of (1) general supportive measures, (2) relief of pain or discomfort, (3) specific drug therapy and (4) local treatment.

1 **GENERAL SUPPORTIVE MEASURES**—During the acute stage the advisability of bed rest depends on the severity of the constitutional symptoms. If these are mild, ambulatory treatment is permissible. Fluid intake should exceed 2000 cc. Many patients limit fluid in an effort to reduce the frequency of urination. This usually defeats its own purpose. Stimulants and irritating foods should be avoided, but otherwise a full diet may be allowed.

2 **MEASURES TO PROMOTE COMFORT**—Occasionally, the pain of cystitis is so severe that morphine may be necessary. Usually, however,

tablets of aspirin, 5 grains, and codeine sulfate,  $\frac{1}{2}$  grain by mouth at intervals of four to six hours, will suffice to relieve the discomfort. Heat applied to the pelvic area by electric pad or hot water bag is very helpful. Perhaps the greatest degree of comfort can be obtained from the hot sitz bath. This should last from fifteen to twenty minutes as the temperature of the water is gradually raised to 115° F. A hot prolonged vaginal douche of saline may be substituted for the sitz bath.

**3 SPECIFIC DRUG THERAPY**—During the past few years, drugs of the sulfa group have largely replaced other agents in the treatment of urinary infections. They are particularly effective in most cases of acute cystitis, as kidney function is not affected and patients are usually able to tolerate the drug in sufficient dosage to control the infection. Clinical experience as well as *in vitro* experiments have shown that high blood concentrations are not necessary and that a urine concentration of 10 mg per 100 cc is bacteriostatic to most of the organisms found in acute bladder infections. A dosage of 0.5 gm three times a day is sufficient to maintain such a level in most instances. There is little choice between sulfathiazole, sulfadiazine and sulfamerazine in this group of cases. The urine should be rendered alkaline by the administration of sodium bicarbonate 10 grains three times a day, and care should be taken to see that anything that might contribute to dehydration is not allowed to occur. *Penicillin* has been disappointing in urinary infection. The most common organism, *Bacillus coli*, is affected only in high concentrations and only to a limited extent. In infections due to gram-positive organisms penicillin is of more value.

For those cases in which the sulfa drugs are not tolerated or are ineffective, a wide choice of other agents is available. *Caprokol* in 0.10 gm capsules administered three times a day has a soothing effect in urinary infections and is bacteriostatic to a variety of organisms. It should be given only after food, and sodium bicarbonate interferes with its action. Fluids should be limited to 1000 cc daily when giving this drug. *Calcium mandelate* is the best form of mandelic acid for routine use. Resistant *Streptococcus faecalis* infections are favorably affected in some cases by this drug. It should be given in dosage of 12 gm daily in four divided doses of 3 gm each. Again, fluids must be limited to 1000 cc daily, thus depriving the patient of the benefit of a large fluid intake so desirable in the treatment of acute infections.

**4 LOCAL TREATMENT**—In general, *extensive instrumentation* is undesirable in acute infections of the urinary tract. In acute bladder infections in the female, however, there is no danger in gently passing a small size, soft rubber catheter. This provides a specimen for bacteriologic study and rules out such conditions as residual urine or urethral obstruction. Following the collection of the specimen, which should consist of the *last* drops of urine rather than the *first*, 1 ounce of 10 per cent argyrol should be instilled into the bladder and allowed to remain.

as long as tolerated. Improvement following this simple procedure is often dramatic.

In many cases with severe symptoms, great relief may be afforded by *constant catheter drainage*, with frequent irrigations using an 0.8 per cent sulfanilamide solution. A closed irrigation and drainage system gives the best results. The catheter is connected to a glass Y tube, one arm of which leads to the drainage tube and bottle while the other arm is connected to the tube from a reservoir containing the irrigating solution. At suitable intervals (every two or three hours) the reservoir tube is unclamped and about 50 cc. of the solution is allowed to run into the bladder, the drainage tube being closed temporarily by pinching with the thumb and finger. Never put the clamp on the drainage tube. Drainage should be maintained for several days.

The usual course of acute cystitis is from four to ten days. If infections persist beyond this time, complications should be suspected and further urological investigation carried out. Apparent recovery should be confirmed by negative smears or cultures at intervals for several weeks.

#### CHRONIC INTERSTITIAL CYSTITIS (HUNNER'S ULCER)

This condition is undoubtedly one of the most distressing maladies affecting the urinary bladder. One reason for this is that it is frequently overlooked owing to the fact that *the urine usually shows no changes*. Furthermore, cystoscopy may fail to reveal the typical bladder changes unless one is alert to find them, hence the name, "elusive ulcer." Formerly considered an uncommon condition, it is now recognized as the cause of many cases of long-standing bladder trouble in which various methods of treatment, often including abdominal surgery, have been tried over many years without relief. It is an inflammatory process involving all layers of the bladder wall, particularly the submucous and muscular coats. The mucosa may show definite small ulcerations or areas of hyperemia which bleed on overdistention of the bladder. The muscular coats are thickened and show marked lymphocytic infiltration.

**Etiology**—The etiology is obscure, and many theories, including that of focal infection, have been advanced. Recently hormonal influences have been mentioned as possible factors. For some years this theory has seemed to the author to be a logical explanation of the occurrence and characteristics of this disease. It is very rare in the male, and in the female the majority of cases occur at or after the menopause. In a series of cases observed by the author in which the condition occurred in women below the menopausal age, the victims, almost without exception, gave a history of radical pelvic surgery, involuntary sterility, dysmenorrhea or other evidences of impaired ovarian or other endo-

crine function Cancer of the bladder is extremely uncommon in the presence of this condition

**Diagnosis**—The characteristic symptoms of interstitial cystitis are *marked frequency of urination* and *pain*. This pain is often relieved by emptying the bladder but sometimes it is continuous regardless of the state of distention of the bladder. It occurs usually in the suprapubic area and is excruciating if the bladder becomes the least bit overdistended. Bizarre types of pain in various parts of the body may be a part of the picture. One patient had pain in the shoulder and back of the neck which was entirely relieved following treatment of the bladder. Pain in the lower abdominal quadrants and occasionally in the loin may be among the complaints. The *frequency* is noteworthy for its *clocklike regularity*, and often is so severe that micturition is necessary several times per hour. Night frequency is as common as day frequency, a point of some value in differentiating this condition from granular urethritis and trigonitis. The symptoms in some cases are affected either favorably or unfavorably by the menstrual cycle. The urine is usually *clear* and *sparkling* and shows no growth on culture. At intervals there may be microscopic hematuria, especially if the urine has been held for a longer period than usual.

The diagnosis can often be made over the telephone. A long history, often of many years' duration, of frequency and pain without changes in the urine should immediately raise the suspicion of Hunner's ulcer. While cystoscopy is the only sure means of diagnosis, a tentative conclusion may be reached by observing the effect of overdistention of the bladder. After the vulva has been cleansed with soap and water a soft rubber catheter is inserted into the bladder and a specimen of urine obtained. If this is clear microscopically, 1 ounce of 1 per cent novocaine solution is instilled and allowed to remain in the bladder for five minutes. It is then withdrawn and the bladder is distended to the point of discomfort with boric solution or sterile water. The fluid is then allowed to run out and the capacity of the bladder measured. This is sometimes as much as 300 cc, but usually does not exceed 180 to 240 cc (6 to 8 ounces). The presence of blood in the last few drops of fluid is strong presumptive evidence of the presence of interstitial cystitis. If the first distention does not produce bleeding, it should be repeated.

**Treatment**—While *electrocoagulation* through the cystoscope under anesthesia is perhaps the most reliable form of treatment, its effects are not permanent nor is it universally successful even as a palliative measure. Relief may be obtained in many cases from *general measures* and simple local treatment. Elimination of irritating items from the diet, rest, correction of focal infections and the liberal use of phenobarbital in nervous patients are among the valuable measures to be advised. In spite of the evidence of endocrine influences in the etiology of this disease, my experience with *hormonal therapy* has been disap-

pointing Individual cases have shown temporary improvement from the administration of various estrogens, adrenal cortical hormone or testosterone, but there has been no uniformity in results Much further clinical trial is necessary before hormonal treatment can be recommended for general use.

*Local treatment*, which has yielded the best results in my experience, consists in the instillation into the bladder of silver nitrate solution in increasing concentration. Treatments may be given as often as three times a week, although results often are as good if the interval is a full week. The bladder is emptied with a soft rubber catheter and 1 ounce of 1 per cent novocaine solution is instilled and allowed to remain five minutes This is withdrawn and an ounce of silver nitrate solution is instilled and retained as long as tolerated A 1:2000 solution is used at first and the strength gradually increased as tolerated, eventually reaching 1 per cent. Improvement is usually gradual but sometimes dramatic If marked relief is not produced within a few weeks the diagnosis should be questioned and further urologic investigation undertaken Tuberculosis of the bladder may produce symptoms similar to those of interstitial cystitis, but there is usually pus in the urine. Symptoms are aggravated by silver nitrate. In doubtful cases, tuberculosis should be ruled out by guinea pig inoculation In extremely severe cases relief may be obtained by diversion of the urinary stream by uretero-intestinal anastomosis

#### CHRONIC GRANULAR URETHRITIS AND TRIGONITIS

This condition often accompanies interstitial cystitis, and perhaps may be a forerunner of fibrous bladder neck obstruction, to be discussed later, but for purposes of classification it will be considered as that group of cases which show *granular, nonsuppurative* inflammation of the posterior third of the urethra and trigone, with or without polypoid changes at the sphincteric margin, but *without urinary obstruction*

*Etiology*—Many theories are held as to etiology Focal infection, particularly *chronic* cervicitis, often accompanies it. Previous specific or other suppurative types of infection may precede it. Tissue changes include congestion and thickening of the entire urethra, and some observers have reported infection of submucosal glands Polypoid changes of various degrees may occur at the bladder neck. Seen cystoscopically the trigone and proximal urethra, both of which are of similar embryological development, show a diffuse granular inflammation, often accompanied by a pseudomembrane occupying part or all of the trigone

*Diagnosis*—The symptoms are *frequency of urination* and less commonly, *burning on urination* Discomfort in the suprapubic regions and groins may be present, but less severe than that due to interstitial cystitis The frequency is less marked at night and may be relieved by lying down. *Urgency* and *slight incontinence* are common



The disease is most frequently seen in the middle years, but has been reported in young girls. Again, the symptoms may be affected by the onset of the menstrual period.

Examination may reveal tenderness in the urethra on palpation and on passage of the catheter. There is no obstruction and no residual urine. Culture may reveal organisms but there is *rarely pus in the urine*. Passage of a sound may give the impression of a "snug urethra."

The tentative diagnosis rests on the day frequency, the tender urethra, the clear urine and the absence of pain on distention. Temporary relief of symptoms by the single passage of a sound often occurs and is of great diagnostic value.

**Treatment**—*General measures* include clearing up of focal infections, such as cervicitis, in addition to dietotherapy and chemotherapy as previously outlined if infection is present. The one local measure of great value is *gradual dilation of the urethra* with metal sounds or dilators. The procedure is less painful if one of the anesthetic jellies is applied via a cotton swab before passing the sound. Treatments should be given at weekly intervals starting with 24 F or 26 F and increasing the size as tolerated. It is important to *overdilate* the urethra, and numerous cases which have seemed resistant have responded to dilation up to 31 F or even 33 F. Instillations of silver nitrate in conjunction with the dilations as recommended for interstitial cystitis are of value.

#### FIBROUS BLADDER NECK OBSTRUCTION

Although, as previously stated, this condition may represent the end result of granular urethritis, it presents a distinct clinical entity inasmuch as some measure of *urinary retention* is usually present. The clinical picture is very similar to that of prostatic obstruction of the fibrous type in the male and the term "female prostate" is quite appropriate. Some observers have found tissue from the bladder neck in the female that closely resembles prostatic tissue. Whether the tissue changes are actually due to glandular hypertrophy or fibrous tissue contracture is not pertinent to the present discussion, as the *presence of obstruction*, whatever may be its nature, is the cause of the symptoms and the secondary changes, which include bladder trabeculation, infection and renal insufficiency, exactly as in prostatic obstruction.

**Diagnosis**—The condition is seen most frequently in the older age group although it may appear at any age. In the early stages the principal symptoms are *urinary frequency* and difficulty in emptying the bladder. Secondary infection is common and aggravates the frequency. Hematuria is not uncommon, but if present it should not be assumed to be due to this condition. Constitutional symptoms, even to various degrees of uremia, may be the first reason for seeking medical care.

On examination, the bladder may be palpable suprapubically. Obstruction to the small catheter is not necessarily present, but *some*

*residual urine is the rule* Examination of the urine shows little unless complicating infection is present The blood nonprotein nitrogen is often elevated

*Treatment*—The correction of this condition depends on the establishment of adequate drainage Often *constant catheter drainage* is necessary as described under the treatment of acute cystitis Dilation of the urethra by sounds may suffice Size 28 F is adequate Secondary infection should be treated by chemotherapy and any uremia by copious intravenous fluids, 5 per cent glucose in saline being the most effective If complete relief of symptoms and elimination of residual urine are not secured by these measures, *transurethral resection of the bladder neck* may be expected to afford complete relief in most cases

### GYNECOLOGIC CONDITIONS

Although a complete discussion of all the gynecologic conditions that may cause urinary symptoms is beyond the scope of this paper, several general observations are pertinent The most important is that essential urinary pathologic change may accompany the pelvic disease and actually be *responsible for the urinary symptoms* The results of pelvic surgery may thus be disappointing For instance, frequency of urination is commonly seen as a symptom of cystocele or prolapsus, but bladder neck obstruction also occurs very frequently in conjunction with cystocele and should be searched for in such cases *Pus in the urine* is rarely cured by gynecologic operations and we have recently seen one case in which repair of a cystocele was done on account of urinary symptoms due to renal tuberculosis Urethral caruncle is often accompanied by changes of a similar nature in the proximal urethra In general, the cause of urinary symptoms should be sought in the urinary tract, before assuming that such symptoms will be relieved by correction of gynecologic conditions

### BIBLIOGRAPHY

- Burns, Edgar Evaluation of Urinary Antiseptics. *South M J.*, 37 320-326 (June) 1944
- Cook, E. N. Recent Advances with Chemotherapy in the Treatment of Infections of the Urinary Tract. *New England J Med.*, 226 187 1942
- Folsom A. I. The Female Urethra. A Clinical and Pathological Study. *J.A.M.A.*, 97 1345 1931
- Hyams, Jos. A. and Weinburg S. R. Hyperplastic Change at the Vesical Neck in the Female. *J Urol.*, 51 149-161 (Feb.) 1944
- Kappel L. Mandelic Acid as Urinary Antiseptic. *J.A.M.A.*, 107 1798, 1936
- Ormond, J. K. Interstitial Cystitis. *J Urol.*, 33 576 1935
- Pearson E. L., Jr. Phenobarbital in Interstitial Cystitis. Personal communication.
- Wharton, Lawrence R. Textbook of Gynecology with a Section on Female Urology. Philadelphia, W. B. Saunders Company 1943

# MANAGEMENT OF THE MEDICAL CONVALESCENT

ROBERT W WILKINS, M D \*

THE successful management of the convalescent patient requires the utmost in both the art and the science of medicine. It necessitates a practical blending of patience, imagination, tact, humor, sympathy and encouragement with the scientific use of therapeutic agents, often over long periods of time. It demands that the physician give attention equally to the physical and to the *emotional* debility produced by disease. For with the weakening of the body during illness there comes an even greater weakening of the will, and with the lowering of physical reserves there is an even more deplorable loss of emotional maturity, that, without question, is the greatest single cause of the perpetuation of invalidism. It is the purpose of this paper to describe some of the lessons learned during the care, both in the hospital and in the home, of convalescent patients who have suffered major medical illnesses.

**1 Convalescence Requires Time**—The period of convalescence demands the time not only of the patient but also of the doctor. No other single therapeutic measure is so valuable to or so valued by the patient as the devotion of an adequate amount of time by his physician. It not only allows the doctor to gain full knowledge of the patient and the effects of his illness, but also permits the patient to discover under the encouragement and guidance of his physician the relative importance of the physical and the emotional aspects of his disease. Thus the physician, himself, as psychiatrists are continually pointing out, becomes a potent therapeutic agent, capable of shortening the total convalescent period and thus eventually saving both himself and his patient much time.

The convalescent patient deserves, in fact, he must have, full opportunity to bring out his complaints, questions, fears and fancies in private conversation with his doctor. The actual interview may be greatly facilitated and shortened by the patient's jotting down during the day anything he may wish to discuss. During the talk he should be encouraged to speak frankly of his troubles—physical, mental and emotional. The psychotherapeutic value of such "mental catharsis" cannot be overemphasized. The attitude of the doctor during the interview should be one of sincere, calm, unhurried and uncriticizing interest.

---

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston

\* Associate Professor of Medicine, Boston University School of Medicine, Physician, Massachusetts Memorial Hospitals, Member, Evans Memorial, Massachusetts Memorial Hospitals

He should inquire after the common complaints, such as headache, backache, insomnia, mental depression, weakness, fatigability, constipation and dysuria, and should attend to any bizarre or vague symptoms that the patient may describe. Such disturbances may be more distressing than those arising from serious pathologic processes and very often they can be relieved by simple remedies, or merely by reassurance or encouragement.

Every physician must discipline himself against slipping into a superficial, breezy or hurried relationship with his patients. During his visits he must steel himself to devote the time necessary for a satisfying discussion. He should come unattended by a coterie of followers, and should settle himself comfortably in a chair, with a manner of complete absorption in the patient and his problems. Incidentally, by so doing, he can give the appearance of spending more time than he actually does. But at best, considerable time must be allotted to this procedure.

2 **Convalescence Should Start Early**—As a matter of fact, convalescence should start with the first visit of the doctor. It should begin merely in a psychological sense, by placing great emphasis on getting well. The physician should speak optimistically of recovery, he should mention his purpose to build up resistance, restore strength, relieve pain and promote activity, even when these objectives may be relatively remote. But in addition, as soon as possible, the convalescence should be physical. Much, perhaps too much, has been written lately about the evils of bed rest. Obviously, physical rest is necessary for the seriously ill patient. But it should be interrupted just as soon and as often as does not actually harm the patient. This is especially true in the case of elderly and of cardiac patients. The dangers of pulmonary complications, particularly hypostatic pneumonia and pulmonary infarction, are minimized by early ambulation. Constipation, dysuria, decubitus ulcer, postural hypotension and muscular and skeletal weakening are avoided by abandoning complete bed rest. But more important even than these is the maintenance and boosting of morale, of hope and of the will to recover by an early initiation of convalescence. Neither fever, pain, cardiac decompensation, weakness nor fatigability should be accepted as absolute contraindications. Even when he cannot be gotten out of bed, the patient should be started on passive and then on active movements. He should be massaged, turned from side to side, raised and lowered in the bed, and passively exercised not only to relieve pressure points and muscular aching, but also to speed the peripheral circulation, promote pulmonary ventilation and drainage, and assist bowel and bladder evacuation. Supplemented early by active muscle tensing, later by limb flexing, and finally by coordinated exercises in bed, the patient can do much to build up his strength for getting out of bed.

3 **Convalescence Must Be Painless**—Perhaps no single symptom is so

distressing and demoralizing to the human organism as pain. It prevents rest and sleep, robs the appetite, retards digestion and elimination, promotes weakness and collapse, and destroys emotional equanimity. It must be abolished. On the other hand, every precaution should be taken to avoid the development of dependency or addiction to drugs.

Physicians are altogether too prone to continue the use of opium derivatives into the period of convalescence. Beside the dangers of addiction, they forget the undesirable side effects of morphine, especially its respiratory depressant and constipating actions. If opiates are necessary for pain, it is well to remember that, dose for dose, dilaudid is ten times as analgesic but *only four times* as depressant as morphine. Thus administered in doses of 0.0005 to 0.006 gm, or  $\frac{1}{120}$  to  $\frac{1}{10}$  grain (one-sixth the dose of morphine), it is more effective as a pain killer but less depressant, and incidentally less constipating. Codeine, dose for dose, is only one-sixth as analgesic and one-fourth as depressant as morphine. Hence, relative to its analgesia it produces slightly more depression than morphine. However, it is less constipating and used in doses of 0.015 to 0.06 gm, or  $\frac{1}{4}$  to 1 grain (six times the dose of morphine), it is better for repeated use. Incidentally, larger doses of codeine than 0.06 gm (1 grain) have no greater analgesic effect, but do have a greater depressant effect.

Demerol, the new synthetic analgesic, is almost as potent as the opiates, and while it may lead to addiction it apparently is much less likely to do so than morphine. Also, it has little or no central nervous or respiratory depressing activity, and no bronchospastic or constipating action. It should at least be tried in substitution for or alternation with the opiates. The dose is 0.03 to 0.2 gm ( $\frac{1}{2}$  to 3 grains).

Many physicians have forgotten the pharmacological fact that simple, safe analgesics, such as acetylsalicylic acid and acetphenetidin, used synergistically become effective pain killers, especially when potentiated by a sedative. For example, the following prescription is very good.

R Pentobarbital	
Acetylsalicylic acid	3
Acetphenetidin	3
Mix, make 20 capsules	3
Label: Take one or two capsules for pain	

The addition of caffeine with sodium benzoate, 5 gm, to the above prescription makes it especially good for headache. Or, the combination of aspirin and phenacetin can be brought up to the necessary analgesic action by the addition of very small doses of opiates, for example.

R Acetylsalicylic acid	6
Acetphenetidin	6
Codeine	6
Mix, make 20 capsules	06
Label: Take one or two capsules for pain	

Those of us in medical practice, much more than our surgical colleagues, are prone to forget the usefulness of the local anesthetics for relieving muscular, arthritic, pleuritic or neuritic pains. Procaine hydrochloride in a 1 to 2 per cent solution, injected at the site of origin or reference may relieve intractable pains when nothing else will. Incidentally, 5 cc of a 0.1 per cent solution of procaine injected slowly intravenously is very good for generalized pruritus.

**4 Convalescence Should be Restful**—The enforced inactivity of the patient often makes true rest and relaxation difficult for him. At night sleep may be fitful and unsatisfying while during the day the hours drag wearily by. At the outset, it may be well for the physician to reassure the patient about the number of hours of sleep he should have, pointing out that seven or eight out of the twenty-four is the *most* he can expect and that if he sleeps during the day, he probably will sleep less at night. Also, the doctor can do much to help the patient arrange a daily schedule in which diversions such as books, the radio, the mail, and a moderate number of brief, cheerful visitors are interspersed with the necessary routine of resting, eating, bathing, eliminating and exercising.

The convalescent period is an excellent time to dust off a discarded hobby or to develop a new one. Nature study, stamp collecting, writing, drawing, sewing or other artistic pastimes, to mention but a few, are within the limits of most convalescent patients. Incidentally, the physician with a hobby can much more enthusiastically recommend one to his patients.

As for sedatives, they must be used with considerable thought and care. It is well for the physician to select from the host of sedative drugs a few with which he can become familiar and upon which he can rely. I have selected the barbiturates, the bromides, chloral hydrate and paraldehyde. These four are effective and relatively safe, and allow sufficient variety to avoid toxicity or habituation. By all odds, the most generally useful of the sedatives are the barbiturates. But again there are so many derivatives that I have selected two: phenobarbital and pentobarbital, for routine use.

The sedative action of all the barbiturates is essentially the same, except for the element of time. Depending on their chemical structure, which makes them more or less stable in the body, the different sedative barbiturates are more or less slowly acting. Phenobarbital, a relatively stable derivative, has a slow, long action, since it must be mainly eliminated by the kidney. Pentobarbital, on the other hand, has a quick, short action, since it is unstable and readily metabolized by the liver. Incidentally, it is well to remember that, in the presence of kidney disease, the long-acting barbiturates may accumulate, while with liver disease the short-acting may do so.

Thus, if a relatively slow, long effect is desired, for example, a 'background' of mild sedation, it may be secured with phenobarbital.

0.015 to 0.03 gm ( $\frac{1}{4}$  to  $\frac{1}{2}$  grain) three times a day For a quicker shorter action, as to aid sleep without leaving a hangover, pentobarbital, 0.05 to 0.2 gm ( $\frac{3}{4}$  to 3 grains) is usually most helpful By a combination of the two agents in the proper dose and sequence almost any sedative effect may be produced

The bromides are milder, slower to act and longer acting than the barbiturates They are eliminated by the kidney (like the chlorides), and tend to accumulate slowly in the body The dangers of chronic bromidism with psychosis, anorexia, constipation and acneiform dermatitis may largely be avoided by alternating the bromides with another sedative at least every month

Chloral hydrate is a neglected sedative It is especially useful as an occasional hypnotic, given in a dose of 0.3 to 0.6 gm (5 to 10 grains) in hot milk, on retiring Paraldehyde is a safe sedative, and can be administered orally, intramuscularly or, with caution, intravenously Its only undesirable characteristics are its odor and its tendency to irritate the lung, where it is largely eliminated The dose is 4 to 10 cc (1 to  $2\frac{1}{2}$  drachms) and it does not require sterilizing when given parenterally

Again I wish to emphasize the sedative effects of reassurance and encouragement of the patient Very frequently he feels misunderstood and unappreciated and fears or resents that the family regard him as a burden and do not recognize his efforts to get well It is advisable to call in the family and explain this situation to them and at the same time to point out to the patient the tendency for the convalescent to develop an infantile craving for sympathy and attention By thus frankly dealing with the patient's fears and resentments, they may be relieved and allow him to relax and rest

**5 During Convalescence Bodily Functions Must Be Regulated Towards Normal**—Most Americans are preoccupied anyway with their bowels and especially so when they become ill, believing that all disease is at least partially due to disturbed bowel function Therefore, for psychological, if for no other reasons, it is necessary to regulate the convalescent patient so as to have regular bowel movements At the same time it is wise to avoid the enema or the cathartic habit As soon as possible, constipating medication should be stopped, the patient should be gotten out of bed, and a diet providing bulk, but not necessarily "roughage," should be instituted Enemas should not be given oftener than every three days, and cathartics should be restricted as much as possible Instead, mineral oil, fruit, and especially adequate amounts of fluid should be used A glass of hot water flavored with sodium chloride or lemon juice may be given before breakfast, to start the desired gastrocolic reflex Patients should be reassured when they do not have daily bowel movements, but their desire to do so is usually so firmly ingrained that the physician has to acquiesce in this matter for the sake of the patient's mental and emotional equanimity

A word on the frequency of rectal impaction among elderly convalescent patients may not be amiss. A rectal examination should be done at least once during the recovery period, and if rectal fecaliths are present, retained oil enemas should be given, followed, if necessary, by digital extraction.

The avoidance of urinary retention, on the one hand, and of retrograde urinary tract infection, on the other, requires forethought. Catheterization should be reserved as a last resort, and whenever possible, patients, especially elderly males, should be allowed to get out of bed to urinate rather than run the risk of infection. If no other course is open, the use of the catheter should be preceded and followed by doses of sulfathiazole, 1 to 2 gm a day, along with forced fluids, while rigid aseptic technic is observed during the procedure.

The care of the skin is particularly important in bedridden patients. Supporting pillows and rubber rings, and frequent massages and changes of position are prophylactic. For the local treatment of decubitus ulcers, continuous wet packs of penicillin, dissolved in normal saline, 250 to 1000 units per cc, is the treatment of choice. Supplemented by 120,000 units a day of parenteral penicillin in divided doses, when there are systemic signs and symptoms, this regimen should clean up the gram-positive infections. For the gram-negative, as well as gram-positive infections, Weinstein's solution of 10 per cent urethane, 1 per cent sulfanilamide in sterile water, as a continuous wet pack is very effective. Packs should be changed every twenty-four hours and surgical débridement should be done whenever necessary.

The appetite should be stimulated if necessary, by the use of the old-fashioned bitter tonics, such as tincture of *nux vomica* and compound tincture of gentian. They may be prescribed together as follows:

℞ Tincture <i>nux vomica</i>	10
Compound tincture gentian	qs 170
Label: A teaspoonful before meals.	

Newer fashioned vitamin preparations of the B group also are valuable.

The diet, of course, must be suited to the patient, but it should not be left to his discretion. Rather, it should be prescribed definitely, preferably by list, in kind, amount and frequency. This reassures the patient and gives him an opportunity to cooperate in promoting his convalescence. At the very least, the doctor should discuss and enumerate what foods should not be eaten. In most convalescent patients, these include fried or fatty foods, pastries, animal and vegetable oils, melons, cucumbers, onions, cabbage and other "rough" or raw vegetables, spices, relishes, mustard and sauces. The diet should include added vitamins, calcium (usually as milk) and protein, as meat, eggs and milk.



6 **Convalescence Must Progress Unremittingly**—In so far as the physician is able to promote it, convalescence should progress without remission. He should gently, but firmly, insist on ever-increasing activity and independence, encouraging and reassuring the patient to avoid invalidism. In general, patients who have had serious illnesses are overcautious and overanxious. They lay great stress on their symptoms, most of which are of little or no significance. Therefore, they need to be told quite definitely and usually quite frequently which symptoms and signs are, and which are not, of any importance. In this way the development of a symptom neurosis may be avoided. Also, the physician should prescribe the amount and kind of exercise, usually insisting on gradually increasing rather than on restricting the patient's activities. It is amazing how much of this type of supportive psychotherapy the convalescent patient may need.

#### SUMMARY

The successful management of medical convalescence requires a great deal of time with especial attention to the details of the psychic and physical debility produced by the acute illness. Convalescence should begin early and progress unremittingly, it should be painless and restful, and should restore not only normal bodily function, but also emotional maturity and independence. Considering the relatively long duration of convalescence and the increasing number of convalescent patients in our aging population, the problem is an immense one, and anything that can be done to shorten the process is eminently worth-while.

## OBESEITY IN CHILDREN

NATHAN B. TALBOT, M D

CLINICIANS dealing with children see a great many patients who are overweight for their height. Of the children who are seen in the out-patient and in-patient departments of the Massachusetts General Hospital, approximately one in ten fall into this group.

**Definition of Obesity**—Though most overweight patients are obese, a careful examination sometimes shows that the extra weight is due to a well developed musculature rather than to an excessive accumulation of adipose tissue. Such muscular individuals though "overweight," do not properly come under the classification of obesity. In fact, if obesity is defined as an accumulation of subcutaneous fat which is excessive with relation to the underlying musculature and bones, then certain children may be obese without being significantly overweight for their height.<sup>1</sup> Generally speaking however, most persons who weigh 20 per cent or more than the normal for their height and age are obese.

### CAUSES OF OBESEITY

**Fundamental Causes**—The evidence now available clearly establishes the fact that obesity is due to an intake of calories which exceeds the caloric requirements for energy metabolism, physical activity and growth (protein anabolism).<sup>2, 3</sup> Thus, in the development of adiposity the two important variables are the caloric intake and the caloric expenditure. A relative increase in the diet or a relative decrease in the energy metabolism, physical activity and/or rate of protein anabolism (growth) will tend to yield a surplus of calories which may be stored as body fat.

Most obesity is due to overeating rather than to a diminished energy expenditure on a normal dietary intake. Not uncommonly patients or their parents will cling tenaciously to the thesis that the quantity of food eaten is not large. However, when this is the case, it is almost always possible to elicit a history of dietary excess at some earlier date. In other words, once a patient has eaten too much and become fat, he will tend to remain so if he is eating a maintenance diet. He will not lose weight until such time as he eats fewer calories than he is expending.

---

From the Department of Pediatrics, Harvard Medical School and the Children's Medical Service, Massachusetts General Hospital, Boston. The observations and points of view recorded here were based upon studies supported by the Commonwealth Fund of New York and the Permanent Charities Fund of Boston.

Assistant Professor of Pediatrics, Harvard Medical School. Assistant Physician, Massachusetts Memorial Hospital.

**Contributing Causes**—A number of different factors may induce overeating. Among these are personality problems,<sup>4, 5</sup> organic lesions of the brain (especially of the hypothalamus)<sup>3</sup> and hypoglycemia.<sup>8</sup> On the other hand, physical inertia, hypometabolism and decreased protein anabolism (slow growth) may be responsible for a decrease in the energy requirements.

Of these factors, the personality ones are by far the most important in the majority of obese boys and girls. Some children tend to nibble at food to help relieve themselves of worry, unhappiness or boredom. Others have become accustomed to tables heavily laden with nutritious foods and to seeing their parents, brothers or sisters take gluttonous servings. Sometimes parents erroneously assume that a large appetite per se ensures good health and therefore urge their children to eat too much. Similarly, parents may not be aware of the normal decline in appetite which may occur at about two years of age when the rapid growth of infancy subsides. Attempts to prevent such a normal decline in appetite has led to the development of adiposity in acquiescent children. In the resistant child the same treatment may result in anorexia and leanness.

The mechanism by which organic brain lesions stimulate the appetite is not clear. For reasons beyond metabolic definition, a reasonable meal does not "satisfy." Hypoglycemia secondary to hyperinsulinism induces hunger in some people, but fails to do so in others. It is rarely a factor in childhood adiposity.

Hypothyroidism (decreased energy metabolism, growth and physical activity) is seldom noted in association with obesity in children.

#### CLINICAL TYPES OF OBESITY IN CHILDREN

While the degree of adiposity is referable to the caloric balance, the distribution of accumulated adipose tissue may be influenced by endogenous factors.

**Simple Obesity**—Over 95 per cent of all fat children fall into this group. The only thing wrong with these children is that for personality or environmental reasons they have eaten too much. Studies have revealed that the majority of these children are only children or the youngest child and that many of them are unwanted. In many families the relationship of the parents is unhappy. Food may have taken on exaggerated importance and may become a substitute for love, security and satisfaction.<sup>4, 5</sup>

A careful survey of the history almost always reveals a period or periods of dietary excess. There is no history suggestive of serious intracranial disease. They are free from symptoms of hypothyroidism. In other words, they are healthy children.

On physical examination fat boys and girls with uncomplicated obesity are usually found to be of average or slightly taller than average stature.<sup>6</sup> They are of normal intelligence, quite a few stand in the



Fig 173—This 5 year old boy is presented as an example of simple obesity. He was of normal weight at 1 year (11.8 kg). From that time on he gained at a steady and very excessive rate so that by the age of 5 years he weighed 44 kg or about 21 kg more than he should weigh. During this period of rapid weight gain he also grew rapidly attaining a height of 125 cm. at the age of 5 (normal 105 to 116 cm). He is fond of bread, potatoes, cakes, cookies, puddings, candy bars and the like. Other members of the family also have hearty appetites for a brother of 13 years weighs 80 kg (175 pounds) a sister of 11 years weighs 48 kg (105 pounds) and his father who is 170 cm. (5 feet 8 inches) tall weighs 100 kg (220 pounds). He is of normal intelligence and is free from symptoms of increased intracranial pressure. There is nothing in the history to suggest hypothyroidism. Aside from the excessive accumulation of subcutaneous tissue and tallness in stature, physical examination is not remarkable. The blood pressure is 120/80. Roentgenograms of the skull show a normal sella turcica and fail to reveal any abnormalities. Roentgenograms of the hand and wrist show that his skeletal development corresponds to the average normal for his chronologic age. The urinary 17 ketosteroid output is 0.6 mg. per day a normal value. By the simple expedient of reducing his intake of starchy foods to one half piece of bread or its equivalent per meal three times a day he is losing weight at the rate of about 0.5 kg (1 pound) per month.

top third of their class at school. Some of these children are found to be only moderately plump while others are extremely fat (see Figs 173 and 174). The excess adipose tissue though generally distributed often accumulates especially in the region of the breasts, hips and lower abdomen. Though the breast regions may thus appear enlarged, palpation usually fails to reveal any true mammary gland development.

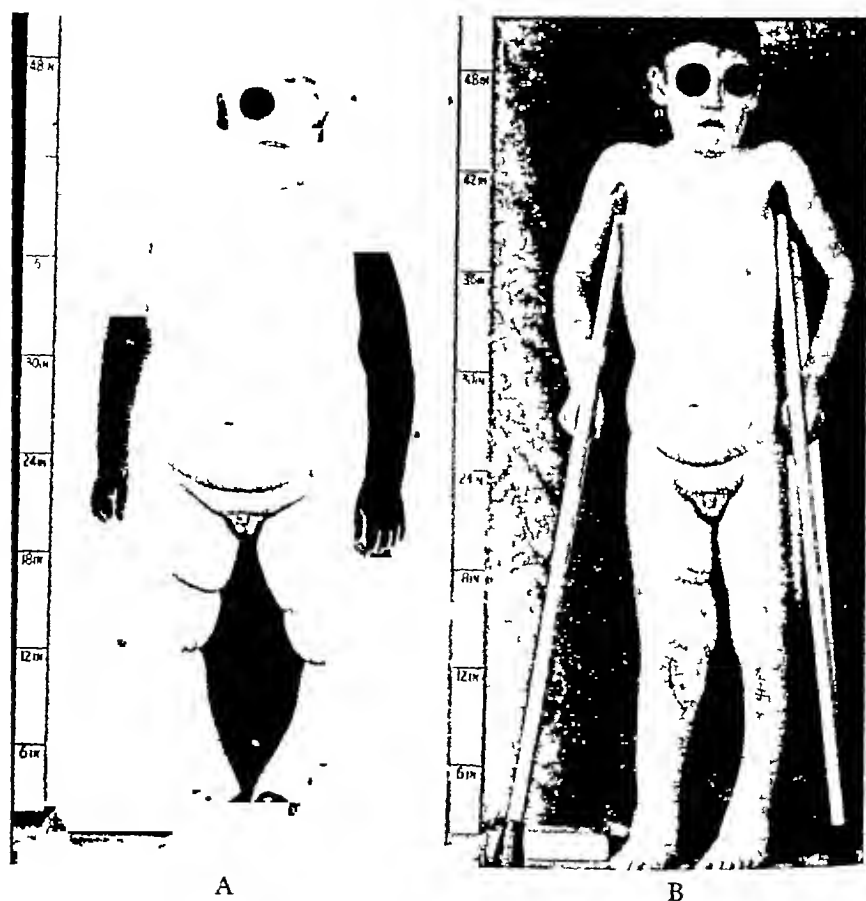


Fig 174—A, Extreme example of simple obesity in a boy of 6 years weighing 65 kg and measuring 126 cm and with genu varum probably secondary to excess weight bearing. During a period of 8 months on a caloric intake of from 1000 to 500 calories per day, he lost 29 kg. B, The administration of thyroid had essentially no effect upon the rate of weight loss. During this period the genu varum was corrected by bilateral osteotomies.

except in adolescent girls. A transient and apparently physiologic development of the mammary tissues is noted in a small number of normal adolescent boys.

The eyes, extraocular movements, visual fields and eyegrounds are normal. While the chest and heart are normal, the blood pressure may be slightly elevated. In this respect it is helpful to remember that the

use of a blood pressure cuff which is too small for the patient's arm will result in an overestimation of the blood pressure. The abdomen is free from abnormal masses. The genitalia in boys often appear to be small because they are embedded in a thick pad of pubic fat. By pressing the fat aside, this erroneous impression can be dispelled. In this connection, it is noteworthy that in normal boys the genitalia remain of essentially infantile size until approximately 11 to 12 years of age.<sup>7</sup> Not until that time do the testes secrete enough male hormone to stimulate any significant development of the masculine secondary sex characteristics. Moreover, some normal boys develop one or two years later than the average. For these reasons boys need not necessarily be considered hypogonad even if genital growth is delayed to the thirteenth or fourteenth year. Sexual development is moderately accelerated in some of these children.<sup>8</sup> The skin is smooth, warm, moist and of normal color. Apparently as a consequence of stretching of the skin striae over the hip regions are occasionally seen. In contrast to the striae of Cushing's syndrome which are purple, these are pinkish white. There is no pathologic hirsutism. The extremities are normal.

in one individual, the resultant combination is sometimes called the Laurence-Moon-Biedl syndrome

Like normal children, these patients are fat because they have eaten relatively too much. It is postulated without much factual basis that these excessive appetite may be due to a hypothalamic lesion.

**Obesity in Association with an Expanding Intracranial Lesion (Fröhlich's Syndrome)**—This is a rare condition usually due to a craniopharyngioma or suprasellar cyst.<sup>15</sup> Children suffering from this disease present

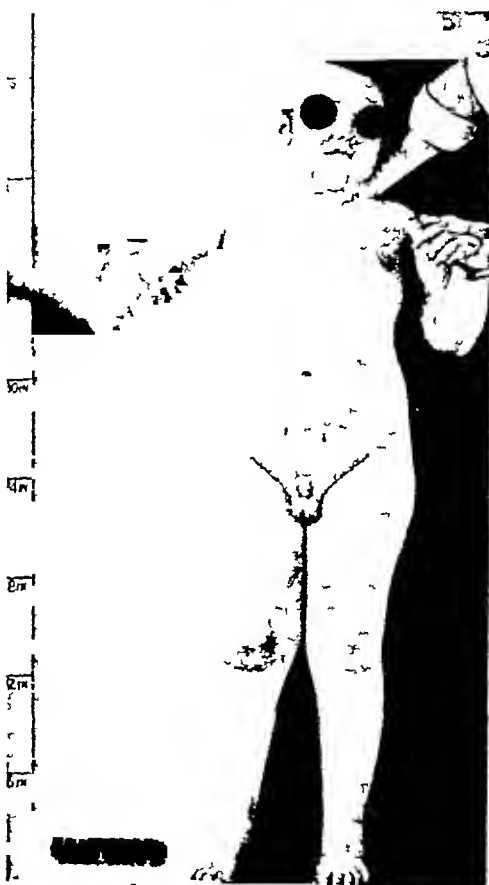


Fig 175 —Obesity in a 9 year old boy with a suprasellar cyst. Note the strabismus

such typical symptoms and signs of an expanding lesion in the region of the optic chiasm as headache, vomiting, disturbances of vision (bitemporal hemianopsia) or of extraocular movements, optic atrophy, separation of the cranial sutures and increased spinal fluid pressure (Fig 175). Roentgenograms of the skull may reveal erosion of the sella turcica or an area of calcification in the neighborhood thereof.

These expanding lesions apparently influence the appetite in much the same manner that experimentally produced hypothalamic lesions

do They may also interfere with the function of the anterior and/or posterior pituitary gland either directly by causing pressure atrophy of the gland or indirectly by interfering with normal neurohypophyseal regulatory mechanisms

When the anterior pituitary function is impaired, various disturbances in growth and development may be noted Interference with the production of the growth hormone results in dwarfism Failure to produce the thyroid-stimulating hormone results in hypothyroidism which leads to retardation in growth and in skeletal maturation When there is failure to produce the anterior pituitary gonad-stimulating hormones, the gonads themselves remain infantile and little or no secondary sexual development occurs Finally, lack of the anterior pituitary adrenal-cortical stimulating hormone results in atrophy of adrenal cortices and the development of Addison's disease In a given patient there may be a complete or only partial impairment in the production of any one or more of these anterior pituitary hormones Hence, patients with destructive lesions in the region of the hypothalamus or the pituitary may present a variety of clinical pictures In fact, certain lesions which affect the hypothalamus but leave the anterior pituitary intact sometimes lead to precocious growth and development Hypothalamic stimulation of the anterior pituitary is believed to be responsible for such precocity

In so far as hypothalamic lesions stimulate polyphagia, they may be considered as factors predisposing to obesity There is no evidence that they induce adiposity by other mechanisms Similarly it is fair to say that there is no such thing as "pituitary" obesity Many patients with destructive lesions of the pituitary actually suffer a marked loss of appetite and as a consequence become cachectic (Simmonds cachexia)

Though the foregoing types of intracranial lesion have received much publicity, other intracranial conditions such as *internal hydrocephalus*, brain tumors, xanthomatosis, pinealoma, syphilis, poroncephaly and postencephalitic changes likewise may lead to obesity and to disturbances in obesity and development

**Obesity in Association with Hypoglycemia**—Hypoglycemia resulting from hyperinsulinism or from glycogen disease induces overeating in some individuals Such conditions as these are but rarely encountered in pediatric practice An abnormally low fasting blood sugar value is suggestive of hyperinsulinism Hepatomegaly, ketonuria and hypoglycemia are suggestive of glycogen storage disease.<sup>10</sup> Patients with this condition show very little elevation of the blood sugar concentration following the administration of adrenalin

**Obesity in Association with Hypothyroidism**—It is unusual to discover hypothyroidism in an obese child This is explained by the fact that hypothyroidism tends to cause a *diminution* in appetite as well as a decrease in the total energy metabolism, physical activity and growth



The most characteristic symptoms of thyroid lack in children are easy fatigability, both physical and mental, constipation, sensitivity to cold weather and slowness in statural growth. On examination almost all hypothyroid children are found to be of dwarfed stature. Mental deficiency is not a consistent finding. The skin is pale, coarse, cool and dry. There is often a subtle appearance of puffiness around the face due to local accumulations of myxedema fluid. Accumulations of myxedema fluid in other localities may also give rise to a pudgy appearance.

Roentgenograms of the hand and wrist reveal a retardation in the skeletal development. In children this diminution in bone growth is associated with a lowered serum phosphatase value (less than 45 Bodansky units per 100 cc)<sup>17</sup>. An elevation in the serum cholesterol concentration above 250 mg per 100 cc is also suggestive. However, in many hypothyroid children who have never received thyroid medication, this value is either normal or low rather than elevated. On the other hand, when such hypothyroid children are given adequate doses of thyroid (1 to 2 grains of USP thyroid daily) for a month or longer and then their medication is discontinued, they develop hypercholesterolemia within the next one to three months. Children with normal thyroid function do not do so.<sup>18</sup> The basal metabolic rate is much less reliable as an index of hypothyroidism in children than in adults. Possibly the best index of thyroid function is the concentration of protein-bound (thyroid hormone) iodine in the plasma or serum. This should receive increasing attention as more laboratories become equipped to make the determination.

**Obesity as Effected by Other Endocrine Disturbances**—Certain steroid hormones of the adrenal cortex and possibly of the sex glands may exert a striking influence upon the distribution of body fat. The outstanding example is *Cushing's syndrome* (Fig 176), a rare condition which is thought to be due to an excess of those adrenal cortical hormones which accelerate gluconeogenesis from protein.<sup>19</sup>

This condition may occur at any age.<sup>20 21</sup> The youngest recorded patient was only eleven weeks old. The incidence is considerably greater in girls than in boys. The obesity is often, not always, of the "buffalo" type. That is, there is a marked accumulation of fat about the head and neck, while the extremities are relatively lean. Muscular weakness is a characteristic finding. The cheeks in the characteristic patient are plethoric in appearance. There are purplish striae in the skin over the hips, abdomen and thighs, acne is common especially in older girl patients. There is often generalized hirsutism. The genitalia may be precociously developed. Hypertension is an outstanding finding. This is reflected by the plethoric appearance already mentioned and may also be manifested by cardiac enlargement and occasionally by cerebral hemorrhages. When the disease is due to an adrenal cortical carcinoma, an abdominal tumor may be palpable.

Intravenous pyelograms may be helpful in revealing such tumors. There is a decreased tolerance for sugar and a tendency to insulin resistance.<sup>10</sup> In some patients there is a marked increase in the urinary excretion of 17-ketosteroids, in others, the values are essentially normal.<sup>10 2-</sup> Osteoporosis of the spine especially is a notable sign. The skeletal development tends to be normal for age and sex.



Fig 176.—Cushing's syndrome in a 12 year old girl. (Courtesy of Dr F Albright.<sup>20</sup>)

Though not so clear-cut, there is also some evidence to suggest that the testicular male hormones favor a distribution of fat in the upper segment of the body while the ovarian female hormones cause the fat to be distributed in the lower body segment. Most preadolescent children show a fairly even distribution of fat when they become obese. Hypogonadism per se does not cause obesity.<sup>2</sup> Obesity, on the other hand occasionally retards the onset of adolescence. In this respect it is of interest that simple weight reduction by dietary means often results in prompt adolescent development in children with simple obesity.

## COMMENTS ON THE CLINICAL STUDY OF OBESE CHILDREN

In view of the fact that obesity, though not a metabolic or endocrine disease per se, may be a sign of some important associated condition, it is desirable to emphasize certain parts of the history and physical examination of fat children. Thus, in the history, symptoms of intracranial disease, physical inactivity, hypometabolism, mental deficiency or family maladjustments may be helpful. In the physical examination, signs of increased intracranial pressure, abnormal eyegrounds, a marked hypertension, an abdominal tumor, skeletal anomalies, a "buffalo" distribution of fat, muscular weakness or shortness of stature may lead to a specific diagnosis.

The value of a careful examination of these patients is well exemplified by one patient who superficially appeared to be a typical example of simple obesity. However, routine examination of the eyegrounds revealed unmistakable papilledema. That child was subsequently found to have a brain tumor.

Roentgenograms of the skull occasionally reveal abnormalities not previously evident. Roentgenograms of the hand and wrist permit an estimation of the skeletal development which is helpful when deviations in the rate of maturation are suspected. Fasting blood sugar determinations as well as glucose and glucose-insulin tolerance tests<sup>23</sup> may be helpful occasionally. Likewise, in the patient suspected of having adrenal cortical disease, a urinary 17-ketosteroid measurement can be diagnostic. Determinations of the basal metabolic rate are seldom helpful and often lead to an erroneous diagnosis of hypothyroidism. Other means for establishing a diagnosis of this disease have been discussed above.

## TREATMENT OF CHILDHOOD OBESITY

**General Considerations**—One of the first considerations in treatment is the question, is it worth while to attempt to reduce the body weight of all fat children? The answer depends partly upon the type and degree of obesity. Because children are growing individuals, it sometimes suffices merely to prevent further gains in weight. A quantity of fat which was moderately excessive for a small child will be normal for the same child when he is a few inches taller. On the other hand, a markedly excessive accumulation of fat may interfere with the physical efficiency of a child to such an extent that participation in normal childhood pursuits is greatly impeded. Furthermore, as mentioned earlier, adiposity per se occasionally retards adolescent development, an occurrence which may cause considerable concern to patients and their parents.

As indicated in the introduction, any person will lose weight when the caloric intake is consistently less than the caloric output. In general, it is more profitable to produce such a caloric deficit through

reducing the caloric intake (underfeeding) than by increasing the caloric expenditures with the aid of exercise and/or medications. It requires a considerable amount of exercise to increase the total caloric output significantly. Thus, even for an adult man weighing 70 kilograms an hour's walk on a level road at a rate of about 3 miles per hour requires only 160 calories or 17 gm. of fat.<sup>24</sup> Vigorous exercise tends to stimulate a voracious appetite. After underfeeding is instituted there may be a one or two week interval before a loss of body weight occurs. This is explained by the fact that while the patient loses fat during this period, he retains an equal weight of water.<sup>2</sup> Sooner or later there is a spontaneous diuresis with the loss of one or more kilograms of weight during the course of a few days. Thereafter weight loss is steady.

How can one induce a child to eat less? In younger children whose diet is completely under the control of their elders, this may not present too great a problem. In the older and more independent child, success depends largely upon gaining the interest and cooperation of the patient. Without these, attempts at therapy are usually a failure. In other words, the problem is a psychological one. Frequently the primary fault lies chiefly with parents who need advice on the management of children. On the other hand, the child often needs to develop pride in his appearance, a feeling of self-confidence and an appetite for something more important than food.

**Dietary Therapy—Regimen A**—This regimen permits eating any reasonable quantities of protein and other relatively low caloric foods while forbidding the eating of certain high caloric items.

1 Eat no candy, cakes, cookies, jams or sugar and no desserts to which such ingredients or flour have been added in any considerable amount.

2 Eat not more than one-half piece of bread (any type) a meal or its equivalent in rice, macaroni, spaghetti, potato or other starchy food.

3 Drink 2 to 3 glasses of skimmed milk a day.

4 Except for these instructions, eat as desired at mealtimes of lean meats, fish, colored vegetables, salads, fresh fruits. Use vinegar or mineral oil dressing. Use ordinary common sense in not stuffing on any particular diet.

5 Plan to eat three reasonable meals a day. The individual who eats no breakfast, a small lunch and a huge dinner tends to gain more weight than the person who eats the same amount of food divided equally between three meals.

In favor of this regimen is its simplicity and the fact that individuals on it are less tempted to eat the forbidden because they feel starved. While it suffices in many instances at least to prevent further weight gains it is ineffective in others. When a more precise adjustment of the caloric intake is desired, diets similar to those of Regimen B may be prescribed.

**Regimen B**—It is appropriate to offer a diet calorically equal to the basal energy metabolism. For practical purposes this may be predicted roughly from the ideal weight for the patient's height as follows.

Height, cm	Ideal Body Weight, kg	Basal Heat Production, Calories per day <sup>26</sup>
73	10	550
115	20	870
137	30	1100
150	40	1250
160	50	1400
170	60	1550

Provided the mineral, nitrogen and vitamin requirements are met, patients suffer no damage from such underfeeding so long as excess body fat remains

Sample diets\* follow

1 750 cal., P 53 gm, F 20 gm, CHO 90 gm

*Breakfast*

- a Orange juice,  $\frac{1}{2}$  cup
- b Toast,  $\frac{1}{2}$  slice, or cereal,  $\frac{1}{2}$  cup
- c Butter or oleomargarine,  $\frac{1}{2}$  square

*Noon*

- a Clear soup (broth, bouillon or consomme) ad lib
- b One egg or lean meat, fish, fowl or cottage cheese, 2 oz. or 5 table-spoons or a piece about  $\frac{1}{2} \times 2 \times 3$  inches
- c Vegetables, 2 servings ( $\frac{1}{2}$  cup each) raw or cooked without sauces
- d Fruit,  $\frac{1}{2}$  cup or equivalent.
- e Skim milk,  $\frac{1}{2}$  cup

*Night*

Same as at noon, but add  $\frac{1}{2}$  slice bread and  $\frac{1}{2}$  square butter

2 1000 cal., P 68 gm., F 30 gm, CHO 115 gm

Add to regimen 1, 1 cup skim milk, 1 slice bread, 1 egg,  $\frac{1}{2}$  square butter

3 1200 cal., P 70 gm, F 51 gm, CHO 115 gm

- \* Substitute  $2\frac{1}{2}$  cups whole milk for the skim milk of regimen 2

The following suggestions as to the choice of foods may be helpful *Vegetables* A serving of potatoes, kidney, lima, navy or soup beans and of corn shall be considered as  $\frac{1}{4}$  instead of  $\frac{1}{2}$  cup Lettuce and celery may be used ad lib All other vegetables equal  $\frac{1}{2}$  cup *Fruits* No sweetened fruit is to be used Unsweetened canned fruits can be purchased A serving of banana is  $\frac{1}{2}$  a small banana *Meats, etc.* All visible fat is removed Ham, pork, bacon, wieners and picnic meats not allowed Obviously fat fish, such as those packed in oil and such as mackerel, shall not be used All cheese except cottage cheese is prohibited *Method of Preparation* Cook all foods without fat unless that allowed for the meal is used Broiling, steaming or boiling is the method of choice for cooking meats No flour gravies or sauces are allowed At least one vegetable a day should be served raw *Other Foods* Prohibited<sup>1</sup>

**Other Therapy**—Benzedrine sulfate (amphetamine sulfate) may be helpful in controlling the appetite It should be given one-half hour before meals The recommended adult dose for chronic medication is usually 10 mg repeated three or four times daily An appropriate fraction of this dose may be given to children Since occasional patients

\* We are indebted to Miss S Wells, dietitian in charge at the Metabolic Ward of the Massachusetts General Hospital, for these diets

are sensitive to the drug and develop cerebral symptoms, the initial dose should be small. A tendency to increased appetite has been noted after discontinuation of the drug and the effect may be only temporary.<sup>70</sup>

Thyroid therapy is disappointing except in the rare obese child who is suffering from hypothyroidism. The administration of this hormone to euthyroid fat children often results in an increased appetite—a reaction which, unless carefully controlled, is clearly undesirable. In sizeable doses it also tends to cause such symptoms and signs of thyrotoxicosis as nervousness, excitability, tachycardia, sweating, tremors, diarrhea and even demineralization of the skeleton and protein depletion.

Obesity is not ordinarily an indication for sex hormone (testosterone, estrogen, etc.) or anterior-pituitary-like (chorionic gonadotropin) therapy. As mentioned above, most fat children mature sexually in a normal manner. In some this process is expedited by simple dietary weight reduction. A discussion of the therapy of significant hypogonadism and of Cushing's syndrome is beyond the scope of this article.

## BIBLIOGRAPHY

- 1 Talbot, N. B., Measurement of Obesity by the Creasurine Coefficient. *Am. J. Dis. Child.*, 55:42, 1938
- 2 Newburgh, L. H., Obesity I Energy Metabolism. *Physiol. Rev.*, 24:18, 1944
- 3 Conn, J. W., Obesity II Etiological Aspects. *Physiol. Rev.*, 24:31, 1944
- 4 (a) Bruch, H., Obesity in Childhood III Physiologic and Psychologic Aspects of the Food Intake of Obese Children. *Am. J. Dis. Child.*, 59:739, 1940
- (b) Bruch, H. and Touraine, G., Obesity in Childhood V The Family Frame of Obese Children. *Psychosomatic Med.*, 2:141, 1940.
- 5 Bronstein, L. P., Wexler, S., Brown, A. W. and Halpern, L. J., Obesity in Childhood Psychologic Studies. *Am. J. Dis. Child.*, 63:238, 1942
- 6 Bruch, H., Obesity in Childhood I Physical Growth and Development of Obese Children. *Am. J. Dis. Child.*, 58:457, 1939
- 7 Schonfeld, W. A., Primary and Secondary Sexual Characteristics Study of their Development in Males from Birth through Maturity with Biometric Study of Penis and Testes. *Am. J. Dis. Child.*, 65:535, 1943
- 8 Talbot, N. B., Butler, A. M., Berman, R. A., Rodriguez, P. M. and MacLachlan, E. A., Excretion of 17-Ketosteroids by Normal and by Abnormal Children. *Am. J. Dis. Child.*, 65:364, 1943
- 9 Talbot, N. B. and Worcester, J., The Basal Metabolism of Obese Children. *J. Pediatr.*, 16:146, 1940
- 10 Warkany, J., Frauenberger, G. S. and Mitchell, A. G., Heredo-familial Deviations I The Laurence Moon Biedl Syndrome. *Am. J. Dis. Child.*, 53:455, 1937
- 11 Warkany, J. and Weaver, T. S., Heredofamilial Deviations II Enlarged Parietal Foramina Combined with Obesity, Hypogonadism, Microphthalmos and Mental Retardation. *Am. J. Dis. Child.*, 60:1147, 1940
- 12 Warkany, J., Nelson, R. C. and Schraffenberger, E., Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency. Use of Varied Diets and of Different Strains of Rats. *Am. J. Dis. Child.*, 64:860, 1942

- 13 Warkany, J Effect of Maternal Rachitogenic Diet on Skeletal Development of Young Rat *Am J Dis Child.*, 66 511, 1943
- 14 Erickson, C A Rubella Early in Pregnancy Causing Congenital Malformations of Eyes and Heart *J Pediat.*, 25 281, 1944
- 15 Bruch, H The Frohlich Syndrome Report of the Original Case *Am J Dis Child*, 58 1282, 1938
- 16 Van Creveld, S Glycogen Disease *Medicine*, 18 1, 1939
- 17 Talbot, N B, Hoeffel, G, Shwachman, H and Tuohy, E L Serum Phosphatase as an Aid in the Diagnosis of Cretinism and Juvenile Hypothyroidism *Am J Dis Child.*, 62 273, 1941
- 18 Wilkins, L and Fleischmann, W Hypothyroidism in Childhood III The Effect of Withdrawal of Thyroid Therapy upon the Serum Cholesterol Relationship of Cholesterol, Basal Metabolic Rate, Weight and Clinical Symptoms *J Clin Endocrinol*, 1 19, 1941
- 19 Albright, F Cushing's Syndrome The Harvey Lecture Series, 38 123, 1942-1943
- 20 Marks, T M., Thomas, J M and Warkany, J Adrenocortical Obesity in Children *Am J Dis Child*, 60-923, 1940
- 21 Farber, J E., Gustina, F J and Postoloff, A V Cushing's Syndrome in Children *Am J Dis Child*, 65 593, 1943
- 22 Talbot, N B and Butler, A M Urinary 17-Ketosteroid Assays in Clinical Medicine *J Clin Endocrinol*, 2 724, 1942
- 23 Fraser, R, Albright, F and Smith, P H Carbohydrate Metabolism The Value of the Glucose Tolerance Test, the Insulin Tolerance Test and the Glucose-Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism *J Clin Endocrinol*, 1 297, 1941
- 24 Lusk, G The Science of Nutrition, 4th ed Philadelphia and London, W B Saunders Co., 1928
- 25 Talbot, F B Basal Metabolism of Children In Practice of Pediatrics, Chapter 22, Volume I, Edited by J Brennemann, Hagerstown, Md., W F Prior Co., Inc, 1944
- 26 Kunstadter, R H Experience with Benzadrine Sulfate in the Management of Obesity in Children *J Pediat.*, 17 490, 1940

## PRACTICAL PSYCHIATRY

HARRY C. SOLOMON, M.D. \*

### NEW METHODS OF THERAPY IN PSYCHIATRIC DISORDERS

THERE are several therapeutic processes that have been developed by psychiatrists and are specially applicable to the field of psychiatry. Therapies of some particular interest may be listed chronologically according to the time of their origination (1) psychotherapy, (2) treatment of neurosyphilis and especially general paresis, (3) insulin shock therapy, (4) convulsive shock therapy, and (5) bilateral cerebral lobotomy. The last three methods may be said to have developed largely on an empirical basis and it has been by the trial and error method that certain conclusions have been reached as to the conditions for which they are most applicable. Enough experience has now accumulated, however, to allow us to make some rather definite statements as to the diagnostic conditions in which each of these five methods of treatment is to be used.

*Psychotherapy*, which may be broadly defined as a method of treatment depending upon the relationship between physician and patient, utilizing the interview method, having many variations in its specific techniques but based primarily on the concepts of a dynamic psychology, has a very broad application to the mental and emotional problems of mankind. However, its most specific values are obtained in personality maladjustments, psychoneurotic manifestations and in somatic disorders in which emotional conflicts play a large role either as the main etiological factor or because of secondary complicating factors (generally named psychosomatic disorders). Psychotherapy to be sure has its place in the treatment of all mental and emotional disturbances, but in many of the psychoses it is hardly an all-sufficient specific methodology.

The treatment of neurosyphilis from the psychiatric standpoint, especially brain syphilis and the specific category of general paresis, depends upon the proper utilization of fever therapy, chemotherapy and penicillin. This problem will not be discussed in the development of this clinical discourse.

*Insulin shock therapy* which was developed by Sakel has proved to be of distinct benefit in the treatment of the schizophrenic disorders. After as long as fifteen years of wide experience with this treatment method the actual value is not definite. However one can assume it has the capacity of improving the prognostic outlook of

Medical Director Boston Psychopathic Hospital Professor of P  
Harvard Medical School, Boston, Massachusetts.



the cases of schizophrenia in its early period. The best figures available at the present time are a result of a careful survey made by a special commission appointed by the Governor of the State of New York. The results of this survey, which compared the outcome of treated cases with a control group as similar as possible but which did not receive insulin shock therapy, indicated that the patients treated had about one and one-half times a greater probability of leaving the hospital greatly improved, if not recovered, that they had a greater chance of remaining well than had the control group, and if they did relapse improvement again was more likely to occur in those originally treated. It may, therefore, be given as a working hypothesis that patients with schizophrenic disorder have a certain recoverable tendency which may be materially increased by this type of treatment.

*Convulsive shock therapy* was originally introduced by von Meduna. Convulsions were produced by the intravenous injection of metrazol. Later a modification of the method of producing the convulsions by passing an electric current through the brain was perfected by Bini and Celletti. Convulsive shock therapy has proved to be of great value in terminating depressive and agitated states. In typical instances of the depressive phase of the manic-depressive psychosis four to twelve convulsive attacks will produce a complete cessation of the disorder in at least 80 per cent of the patients so treated. It also has a considerable value in terminating the disorder in patients in the manic phase. Its value is even more striking in the treatment of patients in the middle and older age groups suffering from agitations. In these patients the normal course of the psychosis is chronicity in almost 50 per cent and a long-continued psychosis of one to four or more years in the remainder, but with the convulsive shock treatment 60 to 70 per cent of these patients are quickly improved. In other words, many who would otherwise be incurable are made well, and many who would have a very long period of mental disorder are returned to good functioning capacity and happy contentment in the course of a few weeks at most.

The *prefrontal lobotomy* operation has not been used long enough nor has it been done in sufficient numbers to indicate with certainty the cases in which it offers the most benefit. Nevertheless, one can state that it offers a high probability of affording relief and returning to a much better status of efficiency and joy of living many of the chronic agitated patients who respond to no other form of treatment. Further, one finds that not a few chronic schizophrenic patients are greatly improved. It also has a distinct value in certain severely disturbed obsessive-compulsive neurotics. Many patients of this latter group in which all other forms of treatment, including long periods of psychotherapy, insulin and convulsive shock therapy had failed, have been greatly improved by the lobotomy operation. This operation, of course, is a very mutilating one which destroys to a considerable extent the integrity of the brain and does some damage to the

personality of the individual. It, therefore, is obviously to be used only when other and simpler methods are not practical, and when the choice between the continuance of the symptoms and the damaging results of the operation favor the latter.

### IMPORTANCE OF CORRECT DIAGNOSIS

From the above discussion it would seem to follow logically that these several methods of treatment are to be used for rather specific types of disorder. It follows therefore, that good diagnostic discrimination becomes an essential in the psychiatric management and treatment of patients. Unfortunately, there are no specific tests except in neurosyphilis which allow for a careful check of clinical diagnosis. Diagnosis must depend in most instances upon the proper evaluation of history, physical and psychiatric examinations. In other words, it depends upon the clinical acumen, experience and judgment of the physician. At this period of the practice of psychiatry when these several methods of treatment are available, none of them being easy, cheap or free from damage, it is obvious that if any one is to be used a high degree of diagnostic skill and first-rate judgment become of the utmost importance.

The remainder of this discussion will attempt to show the importance of correct diagnosis as a preliminary to the application of treatment methods and indicate the seriousness of mistakes.

It has been stated that the convulsive shock therapy is of great benefit in the treatment of depressions and the agitated states. In these conditions psychotherapy has a limited applicability. To be sure there is a considerable amount of difference in the opinion of psychiatrists on this point, but almost all would be in agreement that psychotherapy is a slow, cumbersome and often bad tool in cases of depression during the course of the disorder. On the other hand convulsive shock therapy is probably contraindicated in cases of psychoneurosis. Indeed, in most instances the psychoneurotic rather than benefiting from a course of such treatments is likely to become more tense, more worried, more concerned about himself, which is an addition to the potential dangers inherent in the method. Many times it is extremely difficult to make a differential diagnosis between beginning depression or agitated state and a psychoneurosis. Often the configuration of a depression is that of neurotic symptoms. The following case may well illustrate these points.

*Alex. F.* is a 27 year old woman married to a soldier who was stationed in the Pacific area. She had always been a reasonably well endowed and well adjusted individual, although perhaps unduly dependent upon her strong willed and efficient mother.

She nursed her mother very attentively during a couple of months of a terminal state of carcinomatosis. Following her mother's death she went to live with an aunt who developed a small tumor of the breast, very similar to the

first symptom in her mother's case. Upon our patient developed the responsibility of insisting that her aunt be operated upon. The pathological examination indicated that the growth was benign.

Following this experience our patient began to complain of great fatigue, had disturbed sleep and began to worry about her somatic state. She complained of pains in various parts of her torso, began to fear that she herself had a malignant disease. She was hospitalized for two and one-half weeks in one of our best general hospitals. A painstaking inventory of her anatomy and physiology was made. X-rays, blood tests and almost every known laboratory procedure were given her. At the end of the two and one-half weeks of observation and examinations the diagnosis of psychoneurosis was offered and was confirmed by the psychiatrist.

Rather intensive psychotherapy was carried out by an able psychiatrist for two and one-half months without improvement. It was then considered advisable to transfer her to another psychiatrist who worked with her for several weeks more, when her symptoms became more marked. Agitation became so evident that she was admitted to the Boston Psychopathic Hospital. At the hospital a diagnosis of an agitated depression was made. Consequent upon this diagnosis, convulsive shock therapy was given. At the end of one week, after three convulsive treatments, the patient was greatly relieved, and after nine such treatments the patient was a gay, happy, unconcerned woman, able to take her place at home, with practical freedom from symptoms, and once more enjoying life to the fullest.

It seems indeed probable that had the correct diagnosis been made early, convulsive shock treatment applied at once would have resulted in the prompt alleviation of all symptoms and thereby saved the patient much suffering and disability. It would also have saved many hours of physicians' time. On the other hand, had the diagnosis of psychoneurosis been the correct one it would have been inexcusable to have given convulsive shock therapy.

Perhaps an even more striking case is that of a 53 year old, unmarried woman who came to the Boston Psychopathic Hospital after several months of increasing disability and discomfort. On entrance to the hospital the patient was complaining bitterly of gastric distress, nausea, vomiting and distaste for food. She likewise complained of headache, mild dizziness and generalized aches and pains. She slept very poorly, was constantly requesting sleeping drugs, and even with fair amounts of these slept but little each night. She presented a syndrome with which we are all so familiar, namely that of the complaining, whining, distressed neurotic.

However, we had known this patient at the hospital previously. Twenty years ago she had been a patient here for fourteen months, with rather similar symptomatology. Prolonged and intensive psychotherapy of fourteen months' duration accomplished little or nothing and she left the hospital to remain at home an invalid for another two years, so that her total illness on that occasion lasted more than three years, during which time she was incapable of looking after herself adequately, certainly incapable of work, and suffering much torture.

Nor was this her first disability—in fact, at the age of 16 she had had a long illness diagnosed as a psychoneurosis.

Her history indicated, however, that these disorders, in contrast to the usual story of the typical psychoneurotic, were distinctly delimited, and in the long intervals between these attacks she was a very able, hard-working, energetic person.

Based upon the history of this patient and the total over all picture, the diagnosis on her recent entry to the hospital was that of a depression of manic-depressive type. Indeed this was the final discharge diagnosis twenty years ago, after fourteen months of observation. Therefore without lengthy observation, at the end of approximately a week of hospital stay during which no improvement was attained she was started upon convulsive shock therapy. After two such treatments her sleep improved and she began to show fewer signs of restlessness. In the course of ten days she was relatively comfortable, able to be about the ward taking part in general hospital activities, and at the end of a month she was able to go out and look after herself feeling greatly relieved and once more a hopeful person with an enjoyment of life.

This case illustrates the difficulties of psychotherapy with the depressed patient. It also illustrates the great effectiveness of the convulsive shock therapy in this type of disorder, but, more to the point, it illustrates the diagnostic difficulties in separating the depressive agitated state from that of the anxiety state of the typical psychoneurotic.

If it be true that the psychoneurotic patient does not improve with convulsive shock therapy, which experience seems to indicate is generally the case, and if the majority of the patients in the depressive agitated category respond so well to convulsive shock treatment, it may be assumed that this type of treatment offers diagnostic possibilities. It is probably true that this method might be used as a therapeutic test of diagnosis. Only rarely, however, would this seem to be justified because of the inherent danger of the treatment, and it should not be used unless one has a good basis for belief that it will be beneficial, nor is it by any means a completely satisfactory diagnostic tool, for some patients with a depressive disorder fail to respond adequately to a considerable number of such treatments.

The following case history will document this statement.

Miss V. C. was a young woman of 22 who was taking nursing training when she became uninterested in work and in life. She complained more and more of fatigue. This led to a very careful physical inventory of two weeks duration in a general hospital, at the end of which time a diagnosis of psychoneurosis was forthcoming and on the basis of this diagnosis she was sent to the Boston Psychopathic Hospital for treatment.

She remained at the hospital a number of months, at first being considered as suffering from a psychoneurosis and given quite intensive psychotherapy. As a result of continued study and the lack of progress, the diagnosis was changed to that of manic-depressive depression and she was given ten convulsive shock treatments without notable improvement. Further consideration led to the conclusion that she was suffering from a schizophrenic disorder. On the basis of this diagnosis frontal lobotomy was suggested. The suggestion was not accepted by the family and she left the hospital unimproved. The later course of her disorder indicated strongly that she was indeed suffering from a manic-depressive disorder because she became quite hypomanic and then made a good recovery.

On the case material presented one might perhaps draw two conclusions: (1) that the differential diagnosis between depressions and psychoneuroses is by no means easy to make and (2) that

are frequent disorders. While such assumptions would be unjustified on the basis of this small amount of selected material, yet such are the facts. Mild depressions are more common than most people realize, in fact, they are one of the most common disorders to be met in any clinic due to the fact that the early presenting symptoms are so often related to somatic complaints. The disorder frequently begins with the patient complaining of fatigue, headache, dizziness, visual difficulties, loss of appetite, various gastro-intestinal symptoms, shortness of breath and fear of various diseases. It is unquestionably a fact that many therapeutic successes are more the result of the spontaneous recovery of the depression which has been erroneously diagnosed than of the success of treatment, whether medicinal or psychotherapeutic in kind.

As the last case suggests, the diagnosis of schizophrenia is also often incorrectly made both positively and negatively. Schizophrenia often starts with symptoms that closely resemble the psychoneurosis. It is very common to find a psychoneurotic-like syndrome as the premonitory symptoms of the schizophrenic disorder continuing for many months before the more sinister symptoms are readily evidenced.

M. S. at the age of 17 began to be disturbed about sensations around his heart. In the course of a year he saw several internists who, after careful examination of the cardiac organ, assured him that there was no organic disease. This assurance had no effect upon the patient. He continued to worry and fret about his heart, became more and more concerned therewith, quit work and became increasingly irritable. It finally became evident that he was suffering from schizophrenia. After six years in a state hospital for mental disease, during the latter two of which he was completely mute, a bilateral lobotomy operation was performed, with a moderate degree of improvement. He then told the story that his original concern about his heart was instigated because he believed that he had been damaged through the means of an evil eye.

Although the value of bilateral lobotomy in the treatment of schizophrenia has not as yet been well established, it seems not unlikely that in many instances it is the treatment of choice. An early diagnosis for the proper evaluation of treatment, whether convulsive shock, insulin shock or lobotomy, is as important in this disorder as in any other in the field of medicine.

Diagnosis on which proper selection of therapy depends is important in psychiatry as in other fields of medicine. However, as the delay of a few weeks in the institution of therapy is not of critical importance, one is able to have a considerable period of observation and study of patients before coming to a final decision. During such a period of study one is actually beginning psychotherapy. The relationship of physician and patient is a most important portion of the therapy. Likewise, the interviews which represent an essential and basic part of the examination method are in themselves therapeutic. In the process of the examination the patient has the opportunity to

ventilate many emotional complexes, and often is thereby enabled to gain a considerable amount of insight into his disorder. Repeated diagnostic interviews, which are at the same time of therapeutic value and which require hours of time, are comparable to prolonged study in physical disease which utilizes many laboratory techniques.

Training and experience on the part of the psychiatric diagnostician and therapist are essential if adequate results are to be expected. Any physician who is willing to expend time and energy to study problems in the psychiatric field can fit himself to make diagnoses and to carry out treatment. There is no necromancy in psychiatry. It may be pointed out in this respect that even necromancy takes a great deal of practice before any perfection in the magician's art is attained. Some men because of manual dexterity may excel as surgeons and some men because of their own sensitivities and sympathies may be better psychiatric therapists than others. Nonetheless, every physician can have a considerable competency in diagnosis and treatment in this field. Such competency is an essential for the first-rate practice of comprehensive medicine, and once more it must be emphasized that this can be attained only through training and experience.

It is hoped that the preceding discussion makes clear that inadequate diagnosis can lead to serious errors in regard to human life and happiness.

## ACTIVE IMMUNIZATION AGAINST SOME COMMON COMMUNICABLE DISEASES

MATTHEW A. DEROW, M.D. \* AND SANFORD B. HOOKER, M.D. †

THE number of infectious diseases against which specific protective measures are available is increasing rapidly. In some the need for prophylactic immunization is limited to persons of special occupational or geographical groups. Thus, inoculation against yellow fever is hardly of interest to residents of regions where the specific mosquito vector is absent. Similarly, Rocky Mountain spotted fever is a risk only to those whose occupation or habitat exposes them to possible bites by infected ticks. In others of practically universal distribution eventual exposure to possible infection is likely for almost everyone. Many of these are the so-called "diseases of childhood," essentially because children form the largest group of nonimmunes. Adults are relatively free by virtue of immunity resulting from recovery from the clinical disease or from the stimulus of repeated subclinical infections. Prominent in this category are whooping cough, diphtheria, scarlet fever, measles, chickenpox, typhoid fever and smallpox. In some, particularly typhoid fever, smallpox and diphtheria, the decreased incidence of the disease as a result of improved sanitation and fairly widespread immunization lessens the chance of an adult's being naturally immune and makes imperative the acquisition of protection by artificial active immunization. In still others of comparatively low incidence the very high case-fatality rates make them serious problems in the event of possible infection. Tetanus and rabies are good examples of these.

Of the available procedures, therefore, certain ones stand out as highly desirable for routine application in the population at large. Those considered here are applicable in the prevention of smallpox, diphtheria, whooping cough, scarlet fever, tetanus, the enteric fevers (typhoid and paratyphoid) and rabies. The first five of these diseases are of primary risk to children and protection should be established not later than the twelfth month of life. To delay immunization against these until the child's entry into school is to deny protection when it is most needed, as by far the majority of deaths occur in the pre-school ages. With the present large shifts of population and the habit of vacationing in localities whose state of sanitation may be at best doubtful, more widespread immunization against typhoid and paratyphoid fevers is advisable. Antirabic vaccination is a special prob-

\* Instructor in Bacteriology and Immunology, Boston University School of Medicine, Consultant in Pathology, Norfolk County Hospital, South Braintree

† Professor of Immunology, Boston University School of Medicine, Immunologist, Massachusetts Memorial Hospitals, Member, Evans Memorial, Boston

lem, associated with animals' bites (usually dog bite), that all too commonly confronts the physician

### MEANS OF MINIMIZING THE DISCOMFORT ASSOCIATED WITH INJECTIONS

In carrying out any prophylactic measure a primary objective is to avoid making the subject ill through the attempt to prevent illness. Oversight of this principle is hardly constructive propaganda for universal prophylactic immunization. Attention to certain details, some of them apparently trivial and too often overlooked, can do much to minimize objectionable discomfort associated with injections

1 An all glass 1 cc tuberculin syringe, graduated in hundredths of a cubic centimeter, is best for use in immunization. For skin tests and for measuring fractional doses it is almost indispensable. For the occasional dose greater than 1 cc., the usual 1.5 or 2 cc all-glass syringe graduated in tenths is satisfactory

Needles of 25 or 26 gauge are large enough for any immunizing injection. They must be smooth and sharp. There is no excuse for the use of dull, hooked or rough needles, which only serve to make difficult and painful what should be a simple and often painless procedure.

2 Sterility of syringes and needles must be scrupulously accomplished and maintained. The safest handy method is *boiling* for not less than fifteen or twenty minutes. The syringe and needle should not be assembled until after sterilization. This is best done with a forceps that can be flamed before it touches the sterile instruments. A sterile test tube (boiled with the syringe and needle) for protection of the exposed needle until use is advisable.

The widespread use of alcohol for sterilization of hypodermic syringes and needles is to be deprecated, firstly, because alcohol (even 70 per cent by weight) is at best a poor disinfectant, secondly, because many immunizing agents are injured or destroyed by the traces of alcohol remaining in the syringe and needle, and thirdly, because of the unnecessary pain caused by the injection of even these small amounts of alcohol

3 Practically all immunizing agents are now packaged in rubber-capped vials. The cap must be sterilized by wiping with a potent, non-corrosive skin disinfectant. After the cap has dried, the needle is inserted and a volume of air equal to the amount to be withdrawn is injected. The vial and syringe are then inverted and the required dose is withdrawn. In the case of vaccines or precipitated antigens the material must be well shaken to insure uniformity of the suspension before the required volume is withdrawn

4 Most inoculations are best made in the region of the insertion of the deltoid or triceps muscles. These sites are convenient, and because of the looseness of the surrounding tissues discomfort due to volume



of material introduced, or subsequent slight edema or induration is kept to a minimum. Injections in a series should be alternated from arm to arm so as not to cause irritation by repeated inoculation into the same site. Inadvertent intravascular injection of some materials may give rise to disagreeable (occasionally serious) reactions. To prevent this, tension should be exerted on the plunger of the syringe after insertion of the needle beneath the skin. If blood appears in the hub of the syringe the needle is withdrawn and injection is made at another site.

Preparation of the site of injection requires surgical sterility. Diluted tincture of iodine (wiped off with alcohol to prevent possible burns) or the organomercurial tinctures are satisfactory for this purpose.

5 Individualization of treatment is a *sine qua non* in producing immunity with minimal discomfort to the subject. Printed directions must be considered as general guides to effective dosage, not as rigid, inviolable dicta. Where possible, precautionary tests should be done and as in all medication dosage should be modified in accordance with the age and weight of the patient. Above all, after one dose subsequent doses must be guided more by the previous reactions than by the printed label.

In order intelligently to individualize treatment one must have knowledge not only of technic but also of the nature and mode of action of the materials used. It is from this point of view that the following summaries have been prepared.

#### DIPHTHERIA

**Principle**—Active immunity against diphtheric toxin is produced by the injection of toxoid or toxin-antitoxin.

**Material**—1 *Toxoid* is toxin that has been modified so as to destroy its poisonous properties while retaining its ability to evoke antibody formation. In practice this is usually accomplished by prolonged incubation with dilute formaldehyde. For use in immunization against diphtheria, toxoid is usually standardized to contain 15 L<sub>t</sub> doses per cc., although concentrations as high as 45 L<sub>t</sub> doses per cc. have been used. Diphtheric toxoid may be used unaltered as *fluid toxoid* or as *alum-precipitated toxoid*. The latter is toxoid that has been precipitated with sterile alum to yield a suspension of insoluble alum-toxoid flocules. Toxoid is best kept at 5° C (40° F) but is not rendered dangerous for use by inadvertent freezing.

2 *Toxin-antitoxin* consists of a slightly underneutralized mixture of diphtheric toxin and antitoxin. Most preparations are made with equine antitoxin, but both ovine and caprine sera are in use. Experimental mixtures using human antitoxin have been prepared but have not received widespread trial. The mixture contains 0.1 L<sub>t</sub> dose of

toxin per cc and is usually 80 to 90 per cent neutralized with antitoxin. Toxin-antitoxin mixtures are best stored at 5° C. (40° F). *Under no circumstances should they be allowed to freeze*, as the toxin may thereby be liberated resulting in a highly poisonous product.

**Method—1 Fluid Toxoid**—In young children three subcutaneous injections of 0.5, 1 and 1 cc. at three- to four-week intervals produce immunity in almost all cases. After six months, immunity may be tested by the Schick test. If still susceptible an additional injection of 1 cc. is usually sufficient to produce immunity.

Although not as widely used, the *intracutaneous* injection of 0.1, 0.2 and 0.2 cc. of fluid toxoid at intervals of three weeks apparently produces substantial immunity of long duration.

**2 Alumi-precipitated Toxoid**—Two or preferably three subcutaneous injections of 1 cc. at three- to six-week intervals produce immunity in practically all cases.

Adolescents and adults not uncommonly show local and even systemic reactions to full doses of diphtheric toxoid. It is preferable in these cases to administer only 0.1 cc. of toxoid as a first dose. If no systemic or severe local reaction results the full dosage may be administered for the next two doses. If the reaction be appreciable, subsequent doses should be gauged by the degree of reaction to those preceding. More than three injections will often be required ~~in order~~ to introduce sufficient material to immunize.

**3 Toxin-antitoxin**—Three subcutaneous injections of 1 cc. are administered at one- to two-week intervals. After six months a Schick test should be performed to see if immunity has been ~~acquired~~. If still susceptible the person requires a repetition of the ~~course of~~ injections.

**Comment.**—Toxin-antitoxin used in immunization may ~~lead to~~ sensitization to the foreign serum present in the mixture. In the exception of occasional adults who show severe ~~reactions to~~ ~~injection~~, there are very few indications for the continued use of toxin-antitoxin in diphtheric prophylaxis. Newer preparations ~~are~~ ~~now~~ minimize the amount of bacterial protein present in the ~~mixture~~ and promise practically to eliminate the unfavorable ~~reactions~~ ~~usually~~ ~~seen~~ ~~in~~ use in adults and older children.

## PERTUSSIS

**Principle**—Active immunity is produced by the injection of a suspension of dead bacteria

**Material**—Vaccines are prepared from smooth (Phase I) recently isolated cultures of *Haemophilus pertussis*. The cultures are grown on agar plates or slants enriched with human blood, harvested, and suspended in saline solution containing phenol as a preservative. The concentration of the suspension varies with different laboratories. The vaccines usually available contain

10,000	million organisms per cc	—“single strength”
15,000	“ “ “	—“medium strength”
20,000	“ “ “	—“double strength”
40,000	“ “ “	—“superconcentrate”

Alum-precipitated vaccines are prepared according to the same basic method and then treated with alum to decrease the rate of absorption after injection. These are usually standardized to contain 15,000 million organisms per cc.

In addition to the vaccines described, which have been most widely used, two other preparations are in use. One consists of a suspension of killed *H. pertussis* combined with an “endotoxoid” prepared by treatment of an extract of the organisms. The other is prepared from the soluble toxin of the organism by treatment with formaldehyde to yield a detoxified antigen or toxoid. Both have been reported as satisfactory immunizing agents.

**Method**—A total of 80 to 100,000 million organisms administered in three or four injections over a period of six to eight weeks is required for effective prophylaxis. The actual volume of vaccine varies with the concentration of the preparation used.

1. *Plain Vaccine*—The schedule which follows is for a suspension of 20,000 million organisms per cc. One, 2 and 2 cc injected subcutaneously at intervals of three to four weeks constitute a course. In older children the last dose may be increased to 3 cc (usually divided into two injections of 1.5 cc in each arm). With a more concentrated suspension the volume should be decreased in proportion. More dilute suspensions require an additional dose or two to avoid injections of unduly large volume.

2. *Alum-precipitated Vaccine*—Three doses of 0.5 cc are administered subcutaneously at three- to four-week intervals. Although the total dosage is only 45,000 million organisms the enhanced action of the precipitated vaccine gives rise to a satisfactory immune response.

**Comment**—There is no apparent benefit to be gained by the use of vaccines of low concentration that might outweigh the unavoidable increase in number or size of injections. Reactions following the use of the more concentrated vaccines are neither more frequent nor more severe than those associated with the dilute preparations, whereas the

lesser bulk of the former makes the immediate discomfort of the injection much less objectionable.

Prophylaxis against pertussis, though definitely of value in preventing disease in a large majority of children and markedly alleviating attacks in the remainder, is not comparable to immunization against diphtheria or smallpox in respect to the degree of protection produced. However, a stimulating dose of vaccine two or three years after the primary immunization should suffice to carry most children safely through the period of greatest risk from this disease. A small dose (0.10 to 0.20 cc.) injected intracutaneously merits trial for this purpose.

### RABIES

**Principle**—Active immunity against rabies is produced by the injection of killed or attenuated virus. The usually long incubation period of rabies permits active immunization to be instituted after infection has presumably occurred, and to be completed in time to forestall the development of disease.

**Material**—Rabic vaccine consists of an emulsion of the brain or spinal cord of a rabbit (or other animal) that has been inoculated with "fixed" rabic virus and allowed to become prostrate with the disease. The animal is then killed, usually on the sixth or seventh day after inoculation. The brain and spinal cord are removed aseptically and treated to decrease or destroy the virulence of the virus.

The *Simple phenolized vaccine* (nonvirulent) is prepared by incubating a homogenized suspension of rabbit's brain in salt solution with 1 per cent phenol. After tests for bacterial sterility and residual virulent virus the preparation is kept refrigerated. For use the vaccine is diluted to contain 4 to 5 per cent of brain tissue, 2 cc. of this dilution being a dose. This is the type of vaccine most available and most commonly employed in the United States of America. Nonvirulent vaccines are also prepared by treatment with other reagents such as ether, formaldehyde and chloroform in much the same manner as the Simple vaccine.

The *Pasteur desiccated-cord vaccine* (virulent) is prepared by drying pieces of the spinal cord of rabbits over potassium hydroxide for from two to four days. After desiccation the cord is placed in glycerol and refrigerated. Three to 4 mm. of cord emulsified in 2 to 3 cc. of water or salt solution constitute a dose.

Recent work\* with a dog's brain vaccine, rendered nonvirulent by ultraviolet irradiation, shows it to be a safe immunizing agent, more effective than any of the vaccines in use thus far. As yet it has been used experimentally in dogs only but there is no reason to believe it would prove any less effective in human beings.

**Method**—With the Simple phenolized vaccine fourteen daily injections.

\* Webster L. T. and Casals, J., *Am. J. Pub. Health* 32:268, 1942.

tions of 2 cc usually constitute a course of treatment. In cases with severe bite wounds, especially about the head, seven additional injections are advisable.

Treatment with the Pasteur vaccine consists of sixteen to twenty-five daily injections of vaccine of increasing virulence. The first eight injections use preparations of cord dried four days, the next eight utilize two-day cord, the last nine are usually two- or three-day cord suspensions.

With either preparation the vaccine is administered subcutaneously, usually over the abdomen, the site for each dose being separated as far as possible from that of the previous. A convenient method is to mark off the abdomen into quadrants through the umbilicus, the daily sites being chosen by a clockwise rotation through the quadrants.

**Comment**—Local treatment of the wound is an essential part of prophylaxis against rabies. Cauterization with nitric acid is an effective and time-honoured procedure. However, recent comparative studies\* would indicate that less drastic measures such as thorough cleansing with 20 per cent green soap solution followed by the application of tincture of iodine are probably just as effective. The latter method may well be seriously considered in more superficial bite-wounds especially about the face where the traditional treatment may leave disfiguring scars.

The risk of contracting rabies following the bite of a rabid animal, despite prophylactic immunization, varies from approximately 1 chance in 75 to 1 in 4500 depending on the depth and location of the bite. Wounds on the head are the most dangerous, those on the trunk and legs least so.

The administration of the vaccine (especially attenuated virulent vaccine) is not without a certain risk of its own. The most serious complication of treatment is postvaccinal paralysis, which may be of prolonged duration or even fatal. The incidence of such accidents of treatment is 1 in 3400 with attenuated cord virus and 1 in 8900 to 17,000 with killed vaccines. Paralytic complications seem to be associated with strenuous physical exertion following antirabic prophylaxis, and such patients should be cautioned against undue physical activity. However the treatment should not interfere with the normal daily activities of most people.

(For a comprehensive discussion of the problems of the control of rabies the reader is referred to L. T. Webster's "Rabies," The Macmillan Company, New York, 1942.)

#### TETANUS

**Principle**—Active immunity against tetanal toxin is established by the injection of tetanal toxoid.

**Material**—Toxic filtrates of cultures of *Clostridium tetani* are treated with formaldehyde, yielding tetanal toxoid which lacks the poisonous

\* Shaughnessy, H. J. and Zichus, J. J. A. M. A., 125:528, 1943.

properties of tetanal toxin but retains its specific antigenicity. By using "synthetic" or protein-hydrolysate media for growth of the organisms, extraneous inactive protein remaining in the final product can be kept to a minimum. The toxoid may be used in its original fluid state or as a suspension of very slightly soluble alum-precipitated toxoid.

**Method—1 Fluid toxoid**—Three subcutaneous injections of 1 cc. at three- to four-week intervals constitute an immunizing course.

**2 Alum-precipitated toxoid**—Two subcutaneous injections of 1 cc. at a two- to three-month interval are required.

With either material a stimulating dose of 1 cc. should be administered after one year. A "booster" dose of 0.5 cc. repeated every spring is probably advisable in children and would undoubtedly maintain a high level of immunity.

In case of an injury involving a risk of tetanal infection 0.5 to 1 cc. of toxoid should be administered subcutaneously. There is evidence that *fluid toxoid* is preferable for such "booster" injections following injury because of a more rapid rise in circulating antitoxin than occurs after the use of alum precipitated toxoid.

**Comment**—General or even local reactions other than an immediate stinging sensation at the site of injection are rare. Most severe reactions seem to be associated with sensitivity to peptones that may be present in the material used. In persons sensitive to peptones the use of toxoids prepared from peptone-free culture media is essential, in others it is advisable.

Toxoid can be used for antitetanal prophylaxis following injuries only in persons who have been previously actively immunized. Unimmunized individuals require passive prophylaxis using tetanal antitoxin.

#### TYPHOID AND PARATYPHOID FEVERS

**Principle**—Active antibacterial immunity is produced by the injection of a suspension of dead organisms.

**Material**—The vaccine should consist of a suspension of a killed smooth strain of *Eberthella typhosa* possessing high virulence, good antigenicity and a complete spectrum of antigenic components. The 42-A-58 strain of the U. S. Army Medical School fulfills these requirements and protects against practically any strain of the typhoid organism that may be encountered. The vaccine is standardized to contain 1000 million organisms per cc.

The triple (TAB) vaccine includes strains of paratyphoid A (*Salmonella paratyphi*) and paratyphoid B (*S. schottmülleri*) that have been chosen to fit the criteria given above. The composition of the triple vaccine is as follows:

	1 000 million organisms per cc.			
Typhoid	250	"	"	"
Paratyphoid A	250	"	"	"
Paratyphoid B	250	"	"	"

Vaccines are also prepared containing larger numbers of the paratyphoid organisms

**Method**—The vaccine may be administered either subcutaneously or intracutaneously

1 *Primary vaccination* by the standard *subcutaneous* method requires three injections of 0.5, 1 and 1 cc at weekly intervals

By the *intracutaneous* route primary vaccination requires three injections of 0.10, 0.15 and 0.20 cc at weekly intervals

Primary immunization by either method should be carried out two or three months prior to possible exposure to infection

2 *Subsequent or stimulating* ("booster") courses of injections are required after two or three years to maintain immunity (At least one repeat course is mandatory in the Army)

*Subcutaneous method* Repeat course as outlined above. If practicable one may administer a single dose of 0.5 cc at yearly intervals

*Intracutaneous route* One intracutaneous injection of 0.10 cc (This is accepted by the Army as a complete secondary or stimulating course) It is preferable to repeat this dose every year if the risk of exposure is high

**Comment**—The success of the subcutaneous administration of typhoid vaccine is attested by its use in the armed forces in millions of individuals during the past thirty years. Since the institution of compulsory active immunization, typhoid fever has all but disappeared in the armed forces, whereas the incidence of dysentery which is spread in much the same manner has remained at a constant high level over the same period of time

Severe reactions to the use of the vaccine in this manner are uncommon (under 1 per cent of cases) and usually consist of malaise, fever, anorexia, and rarely chills. Local reactions are more common and may give rise to considerable induration, edema and tenderness at the site of injection

The intracutaneous method of administration has not been used in as many cases or over so long a period of time. Recent well-controlled studies indicate that following primary immunization by this method the absolute height of antibody production is not quite as great as with the older method. However, the immunity induced is probably adequate for protection against all but unusually massive infections. This disadvantage as compared to the subcutaneous route may be overcome by increasing the number of injections or lengthening the interval between injections. Reactions of a systemic nature are extremely rare, and local reactions usually consist of a transient induration, erythema, and slight tenderness at the site of inoculation. The method lends itself well to individual as opposed to mass immunization

## SCARLET FEVER

**Principle**—Active antitoxic immunity is produced by the injection of graded doses of scarlatinal erythroxin

**Material.**—1 The immunizing agent is essentially a filtrate of a broth-culture of scarlatinal hemolytic streptococci. This is then purified to some extent by dialysis and standardized in terms of skin-test doses (STD) For convenience in administration dilutions of 5000 STD per cc. and 50,000 STD per cc. are prepared

2 A relatively insoluble preparation can be made by precipitation of the toxin with tannic acid This is intended for *intracutaneous administration only* and is standardized to contain each of the required doses (750, 3000 and 10 000 STD) in 0.1 cc. An alternative dosage of 500, 2000, 6000 and 10,000 STD per 0.1 cc. is also available

Scarlatinal toxoid has been prepared by treatment of the toxin with formaldehyde, and apparently is a fairly good immunizing agent. However, successful detoxification is not regularly accomplished and as yet scarlatinal toxoid is only in the experimental stage. When the technical problems of preparation have been mastered toxoid will undoubtedly be the reagent of choice from the points of view of number of injections required and freedom from reactions following its administration.

**Method.**—1 *Unmodified Toxin*—A series of graded subcutaneous injections at weekly intervals with a total dosage of 90 to 100,000 STD constitutes an immunizing course. A suggested schedule of dosage is 500, 1500, 3000, 5000, 10,000, 22,500 and 50,000 STD, amounting to 92,500 STD total dosage. With the dilutions mentioned above this consists of 0.1, 0.3, 0.6 cc. of 5000 STD per cc. and 0.1, 0.2, 0.45 and 1 cc. of 50,000 STD per cc. More rapid increases in dosage require fewer injections (five are perhaps the minimum) but entail a high incidence of severe local and often systemic reactions. A longer, more slowly increasing series is often required, especially in adults. The Dick reaction is a fairly reliable guide for choice of the initial dose. Individuals with markedly positive reactions should receive only 100 to 250 STD as a first dose. Subsequent doses are gauged by the reaction to the preceding dose.

A Dick test should be performed one week after the last dose. If it is still positive an additional injection of 50,000 STD usually suffices to convert the Dick reaction to negative.

2 *Tannic Acid Precipitated Toxin*—In children three *intracutaneous* injections of 750, 3000 and 10 000 STD (in 0.1 cc.) at two week intervals constitute a course.

In adults four intracutaneous injections of 500, 2000, 6000 and 10,000 STD (in 0.1 cc.) at two-week intervals are suggested

Immunity may be tested three to four weeks after the last injection by means of the Dick test. If still positive a supplementary dose of 10 000 STD intracutaneously usually suffices to establish immunity.

**Comment**—Any schedule of dosage should be considered as purely



tentative and subject to modification, depending on the reactions of the individual being immunized Slavish adherence to printed schedules negates the basic principle of individualization of treatment, and particularly in the case of scarlatinal prophylaxis has done much to discredit its use because of the uncomfortable and severe reactions that follow ill-advised dosage schedules

The immunity produced by this procedure is *purely antitoxic* in nature and not directed against the streptococcus proper Nevertheless, infections with scarlatinal streptococci in Dick-negative individuals rarely result in mastoiditis, suppurative lymph nodes, nephritism or cardiac involvement—complications that are so common in unmodified scarlet fever One may say that in scarlet fever immunity to one aggressive weapon of the streptococcus is far better than no immunity at all Sulfonamides have proved of tremendous value in the therapy of streptococcal infections, but one must not forget that they have no action against the toxic phase of the disease

#### SMALLPOX

**Principle**—Active immunity against variola is induced by inoculation with a live virus of a related disease (vaccinia)

**Material**—Vaccine virus consists of a homogenized glycerolated suspension of vesicular material from a calf that has been inoculated with vaccinia After a “ripening” interval the vaccine is tested for potency and for the presence of anaerobic and virulent aerobic contaminants Although absolute bacterial sterility is rarely achieved, the number of viable bacteria, chiefly nonvirulent staphylococci, is kept to a minimum by the addition of 0.5 per cent of phenol The vaccine is packaged in sealed capillaries containing sufficient material for one immunization The virus is very sensitive to heat and *must be kept continuously refrigerated, preferably below freezing*, until used The freezing compartment of mechanical refrigerators is ideal for the storage of vaccinal virus

Bacterially sterile virus can be produced by growth on chick embryos However, such cultural methods result in the loss by the virus of some component essential for producing complete immunity in man and other mammals Until this deficiency can be corrected by improved cultural methods, the traditional calf vaccine remains the agent of choice

**Method**—The site of vaccination is prepared by thorough cleansing with soap and water, followed by a volatile antiseptic such as ether, acetone or undenatured 95 per cent alcohol, which is allowed to dry Under no circumstances should a nonvolatile disinfectant such as iodine, organic mercurials (mercurochrome, metaphen, merthiolate) or even denatured alcohol be used in the preparation of the site as the virus is readily inactivated by such reagents resulting in the failure of the vaccination to “take.”

The capillary container having been wiped with ether or acetone, both ends are broken off and the vaccine expressed onto the skin by means of a bulb supplied with the material. The skin is held taut with one hand and firm pressure is applied through the drop of vaccine with the side of the point of a sterile ordinary needle held parallel to the skin surface. Twenty to thirty such strokes over an area not exceeding  $\frac{1}{4}$  inch in diameter suffice to introduce an adequate amount of virus. The pressure of application of the needle should produce a barely visible abrasion and should not draw blood.

After vaccination the excess material may be wiped off gently with sterile gauze. No dressing is required. *Under no circumstances should a "vaccination-shield" be worn.* In children the site may be protected with dry sterile gauze for one or two days to prevent secondary vaccinia due to contamination of the fingers with active virus.

*Comment*—The skin over the insertion of the deltoid muscle is the site of choice for vaccination. Many individuals request vaccination at other presumably less conspicuous sites, such as the thigh, for alleged esthetic reasons. Secondary infection of the vaccination is much more common in such sites, and because of the tenseness of the surrounding tissues primary "takes" are much more painful and temporarily disabling than when performed on the upper arm. The scar following a properly performed vaccination is barely visible forming what has been called a "sanitary dimple," and should hardly be objectionable to the most fastidious esthete.

Three possible reactions may follow successful inoculation with a potent vaccine. By observations two, four and eight days after vaccination these may be identified

- 1 *Primary vaccinia*, in people who have not been previously vaccinated (who have not had smallpox) or who have lost all immunity conferred previously. A small papule appears on the third to fifth day, becoming a vesicle, and developing into a characteristic umbilicated pustule at the height of reaction by the eighth to tenth day. A dark, dry, crust then forms, falling off after one or two weeks to leave an inconspicuous foetated scar.
- 2 *Vaccinoid reaction*, in people who possess some but not complete immunity. The course of events is similar to a primary "take" but at an accelerated rate, the height of reaction being reached in four to seven days.
- 3 *Reaction of immunity*, in people who possess complete immunity. A small, often itchy, reddened area of induration appears within one day, often as soon as eight hours, enlarges somewhat to a maximum in twenty-four to forty-eight hours, and disappears, leaving no scar. Occasionally a minute vesicle may be present at the height of the reaction.

It is seen, thus, that vaccination serves as a test of immunity to smallpox. As a test procedure it is unique in that in people who show no immunity it automatically remedies the defect. Primary vaccination should be performed in the first year of life, and the state of immunity tested by revaccination on entering primary school and high school and at intervals thereafter. Smallpox can be eradicated only by such a program of vaccination and revaccination of the entire population.

In persons with eczema or similar disseminated skin lesions vaccination is best postponed until the skin returns to normal, as generalized vaccinia may follow inoculation. However, *in the face of an epidemic or other likely exposure to smallpox there are no contraindications to vaccination.*

### COMBINED IMMUNIZATION

Simultaneous immunization against more than one disease, using combined antigens, offers certain advantages. The saving in time and the smaller number of injections required are immediately apparent. Moreover there is considerable evidence that the immune response to such combined antigens is often greater against each than when separate inoculations are used. The reactions following administration of mixed preparations are not appreciably greater than those following the usual single antigens (especially in children) and they lend themselves particularly well to routine prophylaxis in pediatric practice. There are at present available a variety of mixtures for such combined immunization. The most widely used of these are

Diphtheric and tetanal toxoids combined

Diphtheric toxoid and pertussis vaccine combined

Diphtheric and tetanal toxoids and pertussis vaccine combined

Tetanal toxoid and typhoid vaccine combined

As an exception, smallpox vaccination which involves the introduction into the body of a live dermatropic virus should preferably be performed alone. Any injury to the skin (even the insertion of a needle) may result in secondary vaccinia at the site of the injury. To guard against such complications, though the risk is perhaps small, other inoculations were best postponed until the height of the vaccinal reaction has passed.

# CONDUCTIVE DEAFNESS AND ITS RELATION TO LYMPHOID HYPERPLASIA OF THE NASOPHARYNX

## Benefits from X-ray Therapy

EDWARD B D NEUHAUSER, M.D.\* AND CHARLES F FERGUSON, M.D.†

ONE of the most important phases of preventive medicine in pediatrics concerns the early recognition and the prompt and proper treatment of children with impairment of hearing. During recent years it has become increasingly apparent that most of the cases of chronic progressive deafness in adults have resulted from unrecognized and untreated defects dating back to childhood. Had these defects been properly treated in their earlier stages before irreversible reactions had occurred, many individuals who are thus so severely handicapped today would otherwise be living normal lives.

Crowe and Baylor<sup>1</sup> have stated that if children in the primary grades of school were given yearly nasopharyngoscopic examinations, and that if proper treatment by radiation of discovered hyperplastic lymphoid tissue were carried out, in the next generation there would be a 50 per cent reduction of adult cases of deafness. When one considers that at the present time in the United States alone there are approximately 15 000,000 deaf or partially deaf individuals, it becomes obvious that by adequate treatment a tremendous number of such individuals could be rescued from a life-long crippling impairment.

Until recent years, when deafness in childhood has been suspected, the only satisfactory treatment at hand was surgical removal of the tonsils and adenoid. This was often performed with very encouraging and often dramatic results, but unfortunately many of these children again developed increasing impairment of hearing which was very often not relieved by secondary adenoidectomy. Many more cases of deafness are being discovered today because of the increased use of the audiometer in schools, clinics, hospitals and physicians' offices. The high incidence of this disease is now just beginning to be appreciated. In 1938 Crowe and Guild<sup>2</sup> made the revolutionary statement that high tone impairment which previously had always been considered the result of a lesion of the cochlea or of the auditory nerve was in reality often the earliest sign of conductive deafness on the basis of partial occlusion of the eustachian orifices by hyperplastic lymphoid tissue.

---

From the Infants and Children's Hospitals of Boston.

\*Instructor in Radiology, Harvard Medical School; Roentgenologist, The Infants and Children's Hospitals of Boston; Roentgenologist, Boston Lying in Hospital.

†Assistant in Otolaryngology, Harvard Medical School. Associate Visiting Otolaryngologist, The Infants and Children's Hospitals of Boston.

Today this has been established as a well-known fact. In such cases the bone conduction may be reduced as well, even before there is much loss of low tones—a phenomenon also previously considered due to nerve deafness. The restoration of adequate ventilation of the middle ear by re-establishing patency of the eustachian tubes often results in a rapid return to normal hearing. This finding is easily demonstrated by the audiometer and tuning fork test. For this reason, many patients who previously had been classified as having a nerve deafness for which there was no satisfactory treatment, now fall into the category of treatable cases with good promise for restoration of normal hearing.

According to Crowe and Burnam,<sup>3</sup> 75 per cent of children who have had adenoidectomy performed before puberty have visible evidence of recurrence of such lymphoid tissue. The lymphoid nodules are an integral part of the mucosa of the pharynx and nasopharynx, and cannot be completely removed by surgery in any case. After the excision of the large mass of adenoid or tonsillar tissue, the small lymphoid follicles tend to hypertrophy, thereby producing the clinical appearance of "granular" pharyngitis or nasopharyngitis. Many of these nodules are in the region of the eustachian orifices or in the actual pharyngeal portion of the eustachian tubes—obviously inaccessible to surgical means. An increase of this tissue as a result either of infection, normal physiologic hypertrophy with growth, or as a response to surgical removal of masses of such tissue will produce partial occlusion of the tube with a resulting chronic tubotympanic catarrh. If left untreated, irreversible changes are produced in the middle ear which result in permanent catarrhal deafness for which there is no adequate treatment. After the age of fifteen years treatment is much less satisfactory because these secondary changes in the middle ear and tube may be so advanced. Therefore, treatment of the lymphoid tissue must be undertaken in childhood before these irreversible changes have occurred. This present discussion concerns the use of some form of radiation to destroy the lymphoid follicles and their lymphocytes.

It has long been known that lymphoid tissue is unusually sensitive to x-radiation and radium and for this reason can be inhibited by very small doses of these agents. The lymphocyte has a definite life cycle just as have cells of the skin, and the old lymphocytes progress outward into the crypts and are phagocytized, with new ones taking their places. Radiation prevents cell division and formation of new lymphocytes (Crowe and Baylor<sup>1</sup>). The germinal centers of the follicles are injured and obliterative changes of the endothelium of both blood vessels and lymphatics are produced (Schenck<sup>4</sup>). The amount of radiation is not sufficient to cause dryness or atrophy of the mucous membrane, it does not cause crusting in the mouth, pharynx or nasopharynx, it produces no skin changes, involvement of the pituitary or other untoward reactions. Repeated treatment, however, may be necessary to hold this tissue in check during the years of active pro-

liferation of lymphoid tissue until adolescence is reached. If adolescence is reached and the eustachian tubes and orifices have been kept patent, the hearing should then remain normal, without necessity for continued treatment in adult life. If this is not done, treatment in adult life will be of no value.

### DIAGNOSIS

In any patient suspected of deafness, the first essential is a complete history. This includes a family history to determine whether deafness in other members of the family has occurred in early life. Familial deafness in early life makes one very suspicious of otosclerosis, which gives a clinical picture of conductive deafness, yet is not helped by radiation. Certain types of congenital deafness also occur in families. The history should also include questions as to serious illnesses such as pneumonia, meningitis, scarlet fever, head injuries, or other factors which might produce a cochlear or nerve lesion.

A complete physical examination also should be done, and this should include a very complete examination of the ear, nose and throat. Nasopharyngoscopy should be performed on all such patients even if the small children may require a general anesthetic for the procedure. Only by direct observation of the nasopharynx can the location of the lymphoid tissue be accurately determined and its relation to the eustachian orifices be ascertained. A large midline mass of adenoid tissue may have no obstructing effect upon the eustachian tubes, whereas a clean vault with hyperplastic nodules around the lips of the tube may produce a very severe type of conductive deafness. Examination of the ears with the aural speculum usually will show retraction of the drums due to closure of the tubes with absorption of contained air. Retraction of the drums produces an increased prominence of the short process and handle of the malleus, with foreshortening of the handle and a diffused light reflex. Shrapnell's membrane is often markedly retracted. In cases of long-standing catarrhal deafness, there may be considerable thickening and dullness of the drums.

The voice tests, including the whispered and spoken voice, will show definite diminution of hearing. Tuning fork tests in conductive deafness will usually show the Weber test (a vibrating tuning fork placed in the center of the head) lateralized to the deaf ear, whereas in nerve deafness the Weber test is usually lateralized to the good ear. The Rinne test (performed by placing a tuning fork over the mastoid process until the instant at which the vibration is no longer perceptible and then replacing it in front of the auditory canal) in the normal ear will give an air conduction in seconds of approximately twice that by the bone conduction. This same ratio is often maintained in nerve deafness even though the air and bone conduction are both decidedly reduced. In the typical conductive deafness, the Rinne test may be reversed so that the bone conduction, although in itself pos-

sibly somewhat diminished, is more prolonged than the air conduction. It is best to use a tuning fork of 256 or 512 frequency, as lower pitched forks will produce too much vibratory sensation as well as sound. These tests should be supplemented by carefully performed audiometer tests. The curve of conductive deafness may be generally depressed throughout all tones, or it may be a low tone deafness with fairly good high tones. As mentioned above, many cases, however, show fairly normal low tones with fairly normal mid tones, but a marked falling off of the higher tones, even though there is no nerve involvement. An abrupt drop in any curve paralleled by a similar marked drop in bone conduction usually suggests a lesion of the cochlea or the nerve. In these cases, radiation is useless.

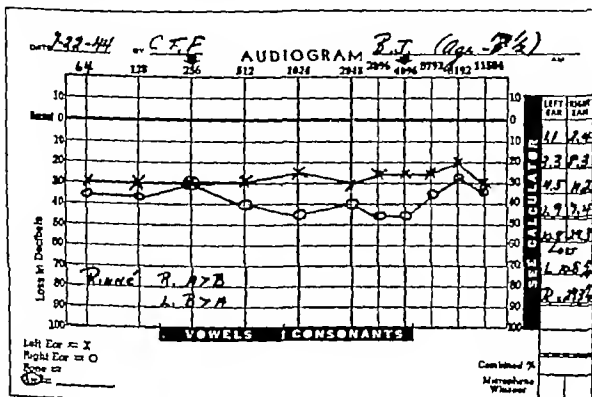
In the average child under four to five years of age, audiometric studies and tuning fork tests are quite unreliable, as considerable concentration and cooperation are necessary for proper evaluation of these tests. In such cases the word of the parent or kindergarten teacher is of great importance as far as the possibility of an existing deafness is concerned. Examination in a strange office may be rather frightening to the apprehensive patient, whereas the mother will know that at home the child cannot hear the radio unless it is very loud and cannot hear family discussions which undoubtedly would otherwise interest him. In such cases, investigation of the nasopharynx is just as important as if audiograms had shown typical conductive deafness curves.

#### TREATMENT

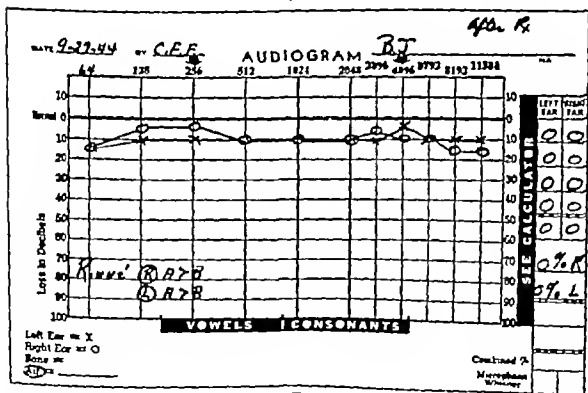
When the diagnosis of conductive deafness due to hyperplastic lymphoid tissue in the nasopharynx has been established, a decision as to the use of surgery or radiation must be made. If there is a sizable mass of adenoid tissue, it is usually best to remove it surgically. If this has already been done, it should be noted whether secondary hypertrophy of lymphoid follicles has occurred. If any of this tissue is present in or about the eustachian orifices where curettage would be impossible or dangerous because of the possibility of producing stenosis of the orifices, then radiation is advisable. Radon applied directly to the nasopharynx has been used in recent years with complete success (Crowe and Burnam,<sup>5</sup> Burnam<sup>6</sup>). Since 1939 we have been employing  $\gamma$ -radiation with equal success, and the efficacy of this form of treatment has been confirmed by other clinics and investigators (Rentschler and Settle,<sup>6</sup> Caruthers<sup>7</sup>). X-ray therapy has several obvious advantages over the use of radium or radon. The necessary equipment is usually available in the smaller communities and hospitals as well as in the larger centers, and little skill or experience is required to obtain a completely satisfactory response, and sedation or anesthesia usually is not necessary.

Thirty-eight patients with conductive deafness have been treated

at the Children's Hospital by x-radiation, but only sixteen have had completely satisfactory follow-ups. In two patients the response was



A



B

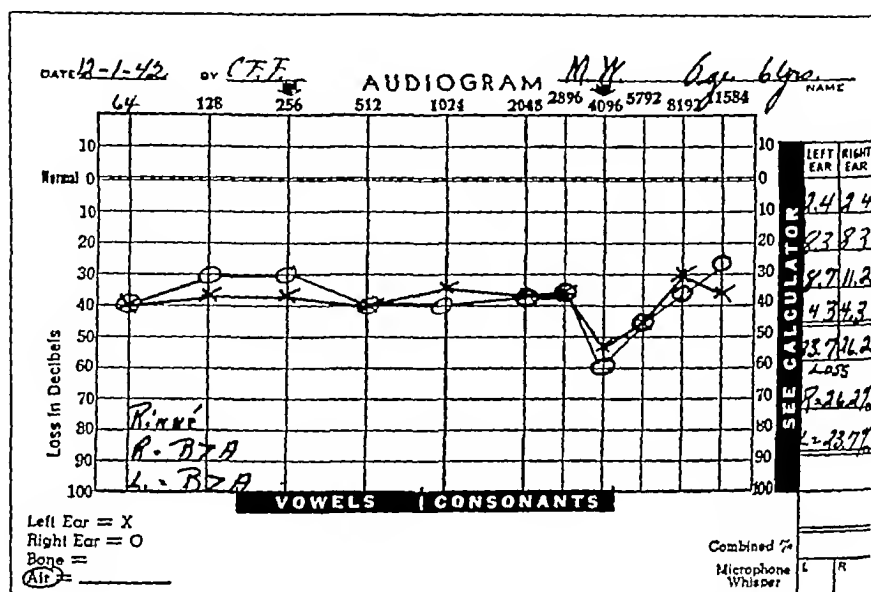
Fig 177—Audiograms showing the status of hearing in a patient, *A*, before and *B* after x ray therapy (Courtesy of Marco Acoustic Instrument Co., Minneapolis, Minn)

not satisfactory. One of these had nerve deafness and was advised only with a vague possibility of improvement. The

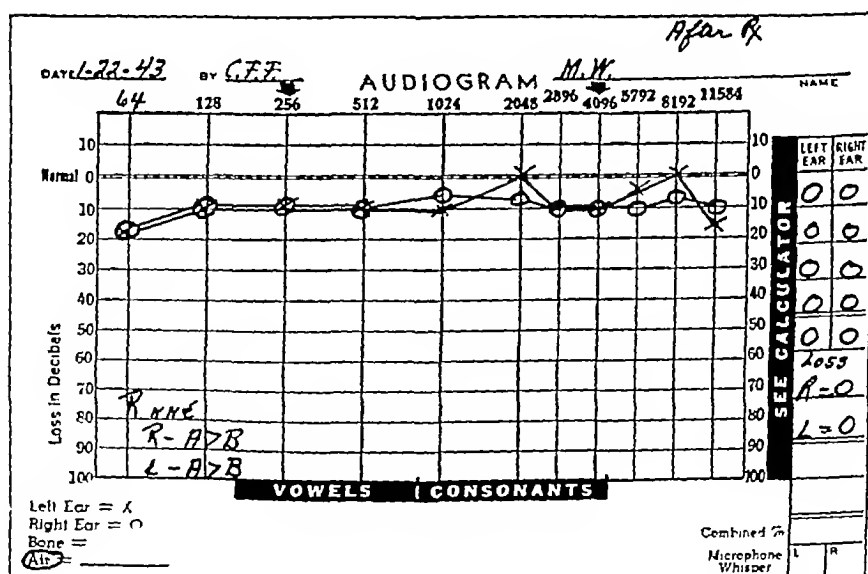
יחזק



a psychoneurotic with complaints of deafness that could never be evaluated. The remaining fourteen all showed improvement, and



A



B

Fig 178—Audiograms of another patient A, before and B, after x-ray therapy (Courtesy of Marco Acoustic Instrument Co., Minneapolis, Minn)

twelve showed an excellent response as seen by accompanying table. Typical audiograms of two patients are shown in Figures 177 and 178

When at the Children's Hospital we first began x-ray treatment of hyperplastic lymphoid tissue, there was considerable variation in the amount of radiation administered and in the number of treatments given. It was our final decision that 800 r measured in air was sufficient to restore the patency of the eustachian orifices and at the present time it is our custom to treat through two lateral ports sufficiently large to cover the nasopharynx, 6 x 8 cm. is usually adequate. At one sitting 200 r is given through each lateral port with the following factors: 200 KV, 10 MA., 50 cm. T.S.D., 1.0 mm. Al, and 0.5 mm. Cu filtration with a HVL of 1.05 mm. of copper. One week later a similar treatment is given and the patient is asked to return in six weeks.

RESULTS FROM X-RAY THERAPY IN SIXTEEN CASES OF CONDUCTIVE DEAFNESS  
DUE TO LYMPHOID HYPERPLASIA OF THE NASOPHARYNX

Patient	Age in Years	Per Cent Loss Preirradiation		Per Cent Loss Postirradiation		Interval between Audiograms	Remarks
		L	R	L	R		
R. B.	10	11	74	0.5	0	2 months	One extra treatment 8 months later because of recurrence.
B. J.	7½	10.8	29.3	0	0	2 months	
A. D.	7½	5.4	3.4	0	0.5	2 months	
E. A.	9	3.0	1.4	0.5	0	3 months	
C. S.	8¼	3.4	17.4	1.0	0	2½ months	Cold at last audiometer test.
S. L. C.	12	0	16.7	1.1	0	4 months	
P. D.	7¼	12.2	3.4	2.0	0	3 months	
B. M.	9	15.0	24.4	1.1	0	5 months	
M. W.	6	21.1	6.6	0	0	7 months	Large perforation of right ear drum. One extra treatment for recurrence. Strong family history of deafness. X-ray tried as last resort. Nerve deafness.
C. R.	10	23.7	26.2	0	0	7 weeks	
G. C.	8¼	4.8	11.5	0	3.8	2 months	
J. F.	6	12.4	18.5	4.8	7.4	2 months	
I. M.	6¼	4.8	7.4	0.0	0.5	1 month later	Psychotic—results not amenable to evaluation. Old mastoid with nerve deafness. Deafness of at least 5 years' duration before treatment.
P. M.	10	18.3	9.6	24.2	19.9	6 months	
D. C.	6	9.5	4.4	1.1	1.1	2 months	
B. L.	10	71.2	0.0	78.7	78.7	2 months	
	6	0	53.6	0	31.6	2 months	
	10	0	66.4	0	41.4	2 months	

Calculations based on Hearing Disability Table (Makco Calculator) released by J.A.M.A., August 1, 1942 (Loss is based on conversation range only)

† See Figure 177.  
† See Figure 178.

for reevaluation and a recording by the audiometer. There have been no unpleasant reactions except that a small percentage of the patients will complain of fullness in the parotid region and show slight swelling of each parotid gland. The patient's family is warned that this may occur within twelve hours after the treatment, but will subside rapidly if an ice bag is applied locally. A few grains of aspirin will control local discomfort due to the swelling.

The importance of the early recognition of conductive deafness and the immediate institution of adequate treatment cannot be overemphasized. It does not appear material whether radium, radon or x-radiation be employed so long as treatment is complete. We recommend

without hesitation the use of x-radiation because of the simplicity of treatment and because of its general availability. We feel that the response has been completely satisfactory, and that if radiation methods were more generally employed, many thousands of cases of permanent, partial or complete deafness could be obviated.

#### SUMMARY

The importance of the early recognition of conductive deafness due to excessive lymphoid tissue in the nasopharynx with blockage of the eustachian tubes has been emphasized.

The criteria for establishing the diagnosis have been elaborated, and the importance of careful audiometer tests has been discussed.

The treatment of this condition by means of roentgen therapy following primary adenoidectomy offers a simple and effective method of controlling most cases of conductive deafness in childhood. X-ray therapy should be available in all hospitals and should be more widely employed.

#### BIBLIOGRAPHY

- 1 Crowe, S J and Baylor, J W Prevention of Deafness J.A.M.A., 112 585-590 (Feb 18) 1939
- 2 Crowe, S J and Guild, S R Impaired Hearing for High Tones A.C.T.A. Oto-Laryng., 26 138-143 1938
- 3 Crowe, S J and Burnam, C F Recognition, Treatment, and Prevention of Hearing Impairment in Children Ann Otol, Rhinol, and Laryngol, 50 15-31 (March) 1941
- 4 Schenck, H P Influence of Nasopharyngeal Hyperplasia on Ear, Histologic Examination of Hyperplastic Lymphoid Follicles after Irradiation Laryngoscope, 51 780-790 (Aug) 1941
- 5 Burnam, C F Irradiation Treatment of Hyperplastic Lymphoid Tissue. Laryngoscope, 50 663-670 (July) 1940
- 6 Rentschler, H D and Settle, J W Jr Treatment of Impaired Hearing by Radiation of Excessive Lymphoid Tissue in the Nasopharynx. Pennsylvania M J., 47 985-988 (July) 1944
- 7 Caruthers, S B X-ray Therapy in Treatment of Deafness Mississippi Doctor, 20 307-314 (Dec) 1942

# THE TREATMENT OF MENINGITIS

JOHN A. V DAVIES, M D

THE treatment of the common forms of meningitis caused by pyogenic bacteria has, with one or two exceptions, progressed rapidly in recent years. We owe this progress largely to the development and application of specific antisera and the chemotherapeutic agents, the sulfonamides and penicillin. Measured in terms of decreasing mortality, there is cause for great satisfaction over the results. Analysis of the survivors in terms of their neurologic state reveals how much remains to be done in order to avoid irreparable damage to the central nervous system.

In the past fifteen years at least 864 patients were treated at the Infants and Children's Hospital of Boston for meningitis due to pyogenic bacteria. The causative organisms were as follows

Organisms	No of Cases
Meningococcus	214
Hemophilus influenzae	190
Mycobacterium tuberculosis	153
Pneumococcus	150
Streptococcus	105
Staphylococcus aureus	31
Endamoeba coli	17
Miscellaneous (Surseuter Proteus, Alcaligenes, Paratyphoid, one each)	4

**Age Incidence**—The incidence of meningitis reaches its peak in infancy. During epidemic years of meningococcal meningitis, children and adults may be attacked in large numbers, but infants retain their unenviable lead. Their lack of resistance to infections in general, their metabolic instability, and the practical difficulties of handling infants and administering treatments enable one to assert that if infants can be cured treatment of adults will be relatively easy. The fact that injury to the growing nervous system projects itself far ahead, perhaps in a widening arc, into adult life, adds to the responsibility of the physician in charge of these patients.

## PREVENTION

A discussion of the treatment of meningitis naturally extends to methods of prevention. Public health measures involving better homes and medical care, avoidance of overcrowding, supervision of school children, separation of the sick from other members of the household, and reduction in the incidence of respiratory infections in general should have a beneficial effect on the incidence of most types of men-

ingitis Prompt recognition and treatment of foci of infection elsewhere in the body may prevent direct or hematogenous extension of the organisms to the meninges

In the case of tuberculous meningitis, which still has a mortality of almost 100 per cent, the above measures are of paramount importance Pending the development of specific remedies, on which a great deal of work is now being done, one can only hope that tuberculosis will be wiped out completely by public health measures

More specific remedies are available to individuals intimately exposed to meningococcic infection Even a small dose of one of the sulfonamides in common use, over a period of three or four days, may be justified One dose of 2 gm of sulfadiazine, for example, is usually sufficient to suppress meningococci in the nasopharynx of adult carriers Institutions faced with an epidemic of meningococcic meningitis may wish to administer a small daily dose of a suitable sulfonamide such as sulfadiazine (approximately one-third to one-fourth the usual therapeutic dose) to its members, as long as the hazard exists

#### DIAGNOSIS

Now that effective therapeutic tools are at hand, the early diagnosis of meningitis is of more than academic importance The sooner these tools are brought to bear on the patient's illness, the better are his or her chances of survival with an intact central nervous system

**Clinical Signs and Symptoms**—The infrequency of meningitis in general practice serves to catch many physicians by surprise, even when the cardinal symptoms and signs, such as fever, headache, nausea, vomiting, stiff neck and back, and a positive Kernig clearly present themselves In infants it is too often the mother who first notices the bulging of the anterior fontanel Inasmuch as meningitis is commonest in infancy it is worth while to emphasize that a bulging fontanel is a prime indication for a diagnostic lumbar puncture Other evidence of meningitis may be equivocal or misleading Often there is a history of a respiratory infection from which the infant is apparently recovering when he has a return of fever and becomes irritable or listless and refuses feedings or vomits repeatedly The patient may be unresponsive Convulsions and twitching of the face or extremities may set in Stiffness of the neck and a positive Kernig sign may be elicited On the other hand, the infant may be in a state of shock, with a subnormal temperature and a normal or low white blood count. The anterior fontanel may even be depressed and the patient limp and exhibit no stiffness of the neck So uncertain and variable are the signs of meningitis in this age group that one should perform a lumbar puncture in every case when a reasonable *suspicion* of meningitis exists

**Laboratory Examinations**—After the history and physical examination, the timing of the procedures will depend on the judgment of the physician in charge Usually the order is as follows

1 *Blood culture and blood count* A blood culture is of value as an indication of the extent of the infection. A positive blood culture offers confirmatory evidence of the type of infection in the meninges. At least one flask should be incubated at partial tension of oxygen.

Urinályses and blood counts should be repeated every two or three days if a sulfonamide is given.

2 *Nasopharyngeal culture*

3 *Lumbar puncture* When an infant is involved, some prefer to hold the patient in a sitting position reclining forward against a firm pillow. A good assistant, who can minimize movement by the patient, is very important. A short-beveled No. 21 needle may be used for infants, depending somewhat on the wishes of the operator. A smaller bore is more easily clogged with fibrin. If the optic disks are choked, an intracranial tumor must be considered. In any case, the lumbar puncture should be performed with caution, lest the brain stem herniate into the foramen magnum.

4 *Urinálalysis*

5 *Laboratory consultation and assistance* The original specimen of spinal fluid should be cultured on ordinary blood agar and on chocolate agar slants. It is customary to allow 5 to 10 drops of spinal fluid to drop directly upon two chocolate agar slants and to incubate one at partial tension of carbon dioxide in, for example, a "candle jar." Additional fluid is taken in one or two sterile test tubes for inoculation of a blood agar plate (the more easily to identify beta hemolytic streptococci) and for a total and a differential cell count (with Wright's stain or methylene blue), a globulin test, a total protein determination (if desired), sugar determinations, and a direct smear.

When organisms are found on smear of the original fluid (centrifuged, if the organisms are scarce) steps should be taken at once to identify them as quickly as possible. If gram negative biscuit-shaped diplococci are seen their relative number and the presence or absence of phagocytosis should be noted as prognostic aids. It is customary to type meningococci. Strangely enough, even experienced physicians may occasionally have difficulty in decolorizing meningococci stained by Gram's method and may confuse them with gram positive cocci. Because of its pleomorphism, *Hemophilus influenzae* is often missed entirely or confused with *Escherichia coli* or the meningococcus.

If organisms resembling *Hemophilus influenzae* or pneumococci are seen on smear a determined effort should be made to type them at once by the Neufeld method of capsular swelling. If *H. influenzae* is suspected but the common strain B is not found the organisms may belong to the less virulent respiratory strain for which antiserum is unnecessary or to one of the other five smooth strains. Type F is occasionally encountered and for this a small amount of antiserum has been developed. Organisms too scarce for immediate typing may be incubated either in the original spinal fluid or in Fildes' broth for four to eight hours and then concentrated by centrifugation at about 2500 r.p.m. for fifteen minutes. The same rule applies to pneumococci which may be grown in broth enriched by serum or blood or in ascitic fluid. In typical cases, pneumococci are present in large numbers in the original spinal fluid.

Organisms found in the original culture should be saved for possible future needs, such as tests of susceptibility to the chemotherapeutic agents employed

*Spinal fluid sugar determinations* may be made in the chemical laboratory or by a rough estimation in the clinical laboratory. If 1, 2, 3, 4 and 5 drops of spinal fluid (from a 1 cc. pipette) are mixed respectively with the contents of five small test tubes, each containing 1 cc. of Benedict's qualitative reagent, and heated in boiling water for five minutes, the presence or absence of even a slight reduction at the end of this time indicates the presence of sugar. One or two drops of normal spinal fluid will usually cause some reduction. In purulent meningitis, the tubes may all remain blue as long as the infection is active. Normal spinal fluid usually contains 60 mg or more of dextrose per 100 cc., provided the blood sugar level is normal.

Alexander has worked out a somewhat more accurate table, as follows

Tube Number	Cerebro-spinal Fluid Added	Reduction of Benedict's Solution					
		+	0	0	0	0	0
1	0.05 cc.	+	0	0	0	0	0
2	0.1 cc.	+	+	0	0	0	0
3	0.15 cc.	+	+	+	0	0	0
4	0.2 cc.	+	+	+	+	0	0
5	0.25 cc.	+	+	+	+	+	0
		Over	40 to	30 to	20 to	10 to	10
Mg of dextrose per 100 cc		50	50	40	30	20	10

*Virus infections of the meninges* are characterized by a tendency toward a lymphocytic cellular response in the cerebrospinal fluid, by a normal sugar content, negative smears and sterile cultures

Whenever *tuberculous meningitis* is suspected, a tuberculin skin test, using a 1:10,000 dilution of Old Tuberculin or one comparable to this of another preparation, should be done at once. If this is negative, proceed with stronger dilutions, up to 0.1 cc. of 1:10 dilution Old Tuberculin. The spinal fluid may be examined by staining the centrifuged sediment or the web which forms for acid-fast bacilli enmeshed in the web. painstaking search on more than one occasion for a total of several hours is usually necessary. Culture and guinea pig inoculation with the centrifuged sediment may provide the only proof of tuberculous meningitis. Anxious relatives and friends press one for an early diagnosis

### TREATMENT

**Supportive Measures**—In fulminating or neglected infections, supportive measures may be life-saving and should at times take precedence over diagnostic and specific therapeutic measures. These include the administration of oxygen (tent, cone or nasal catheter), ether, other intravenous or subcutaneous sedatives to control convulsions, and above all, fluids. If there is evidence of dehydration or a history of persistent vomiting or inanition, intravenous fluids, such as 5 or 10 per cent dextrose in water (10 cc per pound of body weight), followed by a hypodermoclysis of physiological saline solution (10 cc per pound of body weight), are indicated. A continuous intravenous drip, to supply 10 cc per pound per hour, may be advantageous in the more severe cases. When an infant shows evidence of acute cerebral edema, 10 to 20 cc of 50 per cent dextrose solution intravenously may give temporary benefit. In milder infections, diagnostic and spe-

cific therapeutic measures come first but sulfonamides should not be given until the patient has been well hydrated, lest insoluble crystals obstruct the renal tubules. Adequate fluids are probably of greater value than alkalization of the urine in preventing hematuria or anuria.

Other foci of infection should be eradicated whenever possible. They may respond to medical care or they may require surgical interference. The indications for surgery are the usual ones, but in the parameningeal infections—sinusitis, otitis media, mastoiditis, and osteomyelitis of the skull—in case of doubt one should probably operate.

**Specific Treatment**—Specific *antisera*, when given, should be preceded by careful tests for hypersensitivity. Antiserum should not be used for this purpose, lest an antigen antibody reaction in the eye or skin cause a false positive reaction and unnecessarily delay the administration of therapeutic serum. A syringe of adrenalin chloride 1:1000, containing 0.3 to 0.5 cc. should be ready. Antiserum may be given intravenously, slowly, undiluted, or in normal saline by slow infusion or drip so that the full dose is given within two hours. Serum may also be given intramuscularly or half by this route and half intravenously. The intramuscular route is probably less efficient and calls for a larger dose of antiserum.

Adequacy of dosage is determined above all by the clinical condition of the patient and the spinal fluid findings. It is desirable to test the patient's own serum for specific antibodies twelve to twenty-four hours after the administration of therapeutic serum, and at least every other day thereafter until convalescence is definitely established. Practice varies, some clinics requiring demonstrable antibodies in a 1:10 dilution of the patient's serum. Others assay the level in undiluted serum. In severe infections a greater excess of antibody is probably called for but patients have recovered whose own serum, tested by its ability to cause capsular swelling of the specific organism (Neufeld reaction), contained no demonstrable antibodies. Blood for this assay may be collected in capillary tubes after finger puncture.

When horse antiserum has been used, capsular swelling may not appear even with excess of antibody as determined by agglutinins or mouse protection. Furthermore, the Francis intradermal test for a positive balance of pneumococcus antibodies and the comparable Dingle test for *H. influenzae* are less reliable with horse antiserum.

If the infection is stubborn and specific antibodies are no longer demonstrable in the blood stream, it may be necessary to repeat the injection of antiserum, preferably within the first week, lest the patient become hypersensitive to this serum.

*Sulfadiazine* is in most instances the sulfonamide of choice because of its wide bacterial coverage and the fact that what toxic effects it may exhibit do not as a rule cause nervous symptoms which might confuse the picture. It penetrates the blood brain barrier fairly well, although this characteristic may not be of prime importance.



The finding of a predominance of polymorphonuclears and reduced sugar in the initial spinal fluid specimen, even if organisms are not visible on smear, calls for sulfadiazine, pending an exact diagnosis of the causative agent

The route of administration varies. In mild cases of meningitis it may be given orally, but it is probably wise to give at least the first two doses as the sodium salt either intravenously or subcutaneously (up to 5 per cent saline)

The first dose is 0.1 gm per kilogram of body weight (or  $\frac{2}{3}$  gram per pound). This or a larger or smaller dose should be repeated in eight or twelve hours, *depending on the blood level*. Except in the case of meningococcal infections, which respond somewhat more readily than do the other forms, a blood level of at least 10 to 15 mg per 100 cc is desirable until the infection has subsided. Some clinics advocate even higher blood levels. As mentioned previously, an adequate intake of fluids is imperative in order to reduce the likelihood of renal complications.

As soon as the patient can swallow sulfadiazine and retain it, the drug may be given orally in divided doses ranging from 0.15 to 0.3 gm per kilogram of body weight (1 to 2 grains per pound) per day, depending on the blood level desired.

*Penicillin*, when indicated, should be given intramuscularly for at least one week. It should be given intrathecally also for at least five days after the spinal fluid becomes sterile. When the response is slow or there is evidence of localized infection, a longer course should be adopted. Intrathecally it may be injected in concentrations of 1000 to 5000 units per cubic centimeter of physiologic saline, after spinal fluid has been withdrawn. In no case should a greater volume of fluid be injected than was withdrawn. The present trend is toward larger doses. Infants should probably receive 10,000 units twice a day and children and adults at least double this amount, in order to maintain a spinal fluid level of 0.05 Oxford units or more per cubic centimeter at all times.

A localized pocket of infection within the skull, when accessible, should be drained. Should the ventricles contain pus which cannot be drained off by lumbar or cisternal puncture, they may be irrigated with normal saline or Ringer's solution by means of suitable needles inserted through the lateral angles of the anterior fontanel or through burr holes. Penicillin, if indicated by the organism found, is then injected into the ventricles.

**Lumbar Puncture**—So much importance is rightfully attached to the lumbar puncture that a summary of the indications for this procedure may be of value.

1 *Diagnostic*—If the first spinal fluid obtained is normal but the condition still suggests the diagnosis of meningitis, the lumbar puncture should be repeated. If no fluid is obtained, after repeated trial at more

than one level, a cisternal puncture should be done. Failing this, subarachnoid or ventricular puncture may be carried out through the lateral angles of the anterior fontanel of infants or through burr holes in the parietal regions of the skull. Naturally, only those familiar with the required technic should attempt these latter procedures, and the indications must be well established.

2 *The Relief of Intracranial Pressure*—Prolonged high pressure may damage sensitive brain cells irreparably. The ideal arrangement would permit continuous removal of excess cerebrospinal fluid, perhaps by an indwelling spinal needle or small catheter. The restlessness of patients and the accumulation of fibrin are inimical to the success of this device.

During the early stages of treatment, before the inflammation within the meninges has subsided, frequent lumbar punctures may be necessary as long as the pressure at the previous puncture is high or whenever the anterior fontanel bulges or vomiting or headache continues.

The subtotal replacement of cerebrospinal fluid and the inflammatory products of the infection—fibrin and pus as well as the soluble specific capsular carbohydrate of such organisms as *H. influenzae* and pneumococci—by oxygen (or air) early in the course of treatment has some justification and is worthy of careful trial in the more resistant forms of meningitis. The technic is that of a pneumoencephalogram. Oxygen is to be preferred, since it is more rapidly absorbed, giving way to fresh spinal fluid. Late in the course of the disease this procedure would seem to offer very little. Although in our hands this treatment has not caused exitus, it is followed by some symptoms of shock and should be reserved for those forms of meningitis relatively resistant to available therapy.

3 *Intrathecal Treatment*—The Infants' and Children's Hospitals of Boston were among the first to discontinue the administration of intrathecal serum, because of its tendency to increase the inflammatory reaction and thereby promote adhesions and the pocketing of pus within the subarachnoid space. The rare exceptions to this rule will be taken up later.

Penicillin unlike the sulfonamides, is not inhibited by pus and causes very little reaction when injected intrathecally. The blood brain barrier serves to keep it out of the subarachnoid space even when there is a good blood level. On the other hand, it disappears within one or two days (depending on the individual case) from the subarachnoid space, and must be reinjected intrathecally at intervals of twelve to twenty-four hours for maximum effectiveness. Except in mild infection a spinal fluid level of penicillin should be determined daily during the infection.

on of heparin (or a comparable anticoagulant) more in normal saline every twenty-four have theoretical advantages in the di

The finding of a predominance of polymorphonuclears and reduced sugar in the initial spinal fluid specimen, even if organisms are not visible on smear, calls for sulfadiazine, pending an exact diagnosis of the causative agent

The route of administration varies. In mild cases of meningitis it may be given orally, but it is probably wise to give at least the first two doses as the sodium salt either intravenously or subcutaneously (up to 5 per cent saline)

The first dose is 0.1 gm per kilogram of body weight (or  $\frac{2}{3}$  grain per pound). This or a larger or smaller dose should be repeated in eight or twelve hours, *depending on the blood level*. Except in the case of meningococcal infections, which respond somewhat more readily than do the other forms, a blood level of at least 10 to 15 mg per 100 cc is desirable until the infection has subsided. Some clinics advocate even higher blood levels. As mentioned previously, an adequate intake of fluids is imperative in order to reduce the likelihood of renal complications.

As soon as the patient can swallow sulfadiazine and retain it, the drug may be given orally in divided doses ranging from 0.15 to 0.3 gm per kilogram of body weight (1 to 2 grains per pound) per day, depending on the blood level desired.

*Penicillin*, when indicated, should be given intramuscularly for at least one week. It should be given intrathecally also for at least five days after the spinal fluid becomes sterile. When the response is slow or there is evidence of localized infection, a longer course should be adopted. Intrathecally it may be injected in concentrations of 1000 to 5000 units per cubic centimeter of physiologic saline, after spinal fluid has been withdrawn. In no case should a greater volume of fluid be injected than was withdrawn. The present trend is toward larger doses. Infants should probably receive 10,000 units twice a day and children and adults at least double this amount, in order to maintain a spinal fluid level of 0.05 Oxford units or more per cubic centimeter at all times.

A localized pocket of infection within the skull, when accessible, should be drained. Should the ventricles contain pus which cannot be drained off by lumbar or cisternal puncture, they may be irrigated with normal saline or Ringer's solution by means of suitable needles inserted through the lateral angles of the anterior fontanel or through burr holes. Penicillin, if indicated by the organism found, is then injected into the ventricles.

**Lumbar Puncture**—So much importance is rightfully attached to the lumbar puncture that a summary of the indications for this procedure may be of value.

1 *Diagnostic*—If the first spinal fluid obtained is normal but the condition still suggests the diagnosis of meningitis, the lumbar puncture should be repeated. If no fluid is obtained, after repeated trial at more

than one level, a cisternal puncture should be done. Failing this, subarachnoid or ventricular puncture may be carried out through the lateral angles of the anterior fontanel of infants or through burr holes in the parietal regions of the skull. Naturally, only those familiar with the required technic should attempt these latter procedures, and the indications must be well established.

2 *The Relief of Intracranial Pressure*—Prolonged high pressure may damage sensitive brain cells irreparably. The ideal arrangement would permit continuous removal of excess cerebrospinal fluid, perhaps by an indwelling spinal needle or small catheter. The restlessness of patients and the accumulation of fibrin are inimical to the success of this device.

During the early stages of treatment, before the inflammation within the meninges has subsided, frequent lumbar punctures may be necessary as long as the pressure at the previous puncture is high or whenever the anterior fontanel bulges or vomiting or headache continues.

The subtotal replacement of cerebrospinal fluid and the inflammatory products of the infection—fibrin and pus as well as the soluble specific capsular carbohydrate of such organisms as *H. influenzae* and pneumococci—by oxygen (or air) early in the course of treatment has some justification and is worthy of careful trial in the more resistant forms of meningitis. The technic is that of a pneumoencephalogram. Oxygen is to be preferred, since it is more rapidly absorbed, giving way to fresh spinal fluid. Late in the course of the disease this procedure would seem to offer very little. Although in our hands this treatment has not caused exsitus, it is followed by some symptoms of shock and should be reserved for those forms of meningitis relatively resistant to available therapy.

3 *Intrathecal Treatment*—The Infants' and Children's Hospitals of Boston were among the first to discontinue the administration of intrathecal serum, because of its tendency to increase the inflammatory reaction and thereby promote adhesions and the pocketing of pus within the subarachnoid space. The rare exceptions to this rule will be taken up later.

Penicillin, unlike the sulfonamides, is not inhibited by pus and causes very little reaction when injected intrathecally. The blood brain barrier serves to keep it out of the subarachnoid space even when there is a good blood level. On the other hand, it disappears within one or two days (depending on the individual case) from the subarachnoid space, and must be reinjected intrathecally at intervals of twelve to twenty-four hours for maximum effectiveness. Except in mild infections, a spinal fluid level of penicillin should be determined daily during the critical stages of the infection.

The intrathecal injection of heparin (or a comparable anticoagulant) in 1 cc. doses of 10 mg. or more in normal saline every twenty-four to forty-eight hours appears to have theoretical advantages in the di-

rection of delaying the formation of fibrinous adhesions. The exact dosage and interval has not been worked out, nor the possible combination of this method with oral dicoumarin or intravenous heparin. Their maximum effectiveness would appear to be early rather than late in the course of the disease.

4 *Observation of the Results of Treatment*—Of course the clinical response of the patient is of great value but it may lag several days behind cerebrospinal fluid signs of improvement. These signs are (1) fall of total protein and rise of sugar levels, (2) fall of white cell count and increase in relative number of lymphocytes, (3) disappearance of organisms from the smear, and (4) sterile cultures.

*Treatment of Particular Types of Meningitis*—With these general outlines of treatment in mind and at the risk of being somewhat dogmatic, one may specify certain measures applicable to particular types of meningitis. Admittedly, therapy is in a state of flux and continuous improvement. What seems up-to-date today may soon need revising the light of later discoveries.

*Meningococcal Meningitis*—This usually responds well to all the commoner sulfonamides. In fact, after adequate dosage of a sulfonamide, the spinal fluid is usually sterile within six to eight hours. If the response is delayed one should consider the possibility of sulfonamide resistance or a pocketing of pus within the subarachnoid space or inside the ventricles. The latter contingencies are commoner in infants. If the organism is sulfonamide-resistant, intrathecal or even intraventricular, penicillin may be substituted. Intravenous antiserum is very rarely necessary, except possibly in infants.

Five days after the spinal fluid becomes sterile and otherwise shows signs of improvement, sulfonamide therapy may be discontinued provided the general condition of the patient corroborates the laboratory findings. One should be particularly conservative in interpreting signs of improvement in infants who were sick more than three days before therapy was instituted or who responded slowly to treatment.

*Influenzal Meningitis*—If the meningitis is caused by a respiratory strain of *Hemophilus influenzae* of relatively low virulence, spinal fluid drainage by lumbar puncture, possibly combined with sulfadiazine, is probably sufficient.

If the strain is type B, sulfadiazine and specific antiserum are indicated. Even in "mild" cases it seems wise to give antiserum without delay. While concentrated horse serum (Massachusetts State) intramuscularly in large doses (180 cc) has cured children with meningitis quite promptly, at present intravenous rabbit serum (Squibb)\* is the method of choice. It has been standardized in terms of precipitable antibody nitrogen, each vial containing 25 mg.

Mild cases should receive at least 50 mg and severe cases 150 mg.

\* Lederle may soon have a similar rabbit antiserum available commercially.

as the initial dose. Alexander suggests that the severity of the infection is best judged by the spinal fluid sugar level. When, by virtue of some degree of immunity or the inhibitory action of sulfadiazine on the organisms, the patient has been ill with meningitis a week or more, less serum may be required to effect a cure or localization of the infection.

Meningitis caused by *H. influenzae* type F has been encountered twice in this clinic, as contrasted with approximately 180 cases caused by type B. One was cured by type F rabbit antiserum.\*

Sulfadiazine should be continued at least two weeks after the spinal fluid has become sterile.

In a few instances, improvement follows the administration of the above measures, but spinal fluid cultures continue to show organisms in small numbers. The intrathecal injection of 1 to 5 cc. of rabbit antiserum after spinal fluid has been withdrawn or after the latter has been largely displaced by oxygen, may bring about a walling off and ultimate cure of the infection.

*Tuberculous Meningitis*—Although several antibiotic agents have been brought forward for use against tuberculous infections in human patients, none are of proved value. Symptomatic treatment of the patient is in order, however, and the most promising of the newer agents, such as streptomycin, may be given a trial.

*Pneumococcal Meningitis*—The treatment consists of sulfadiazine in doses sufficient to maintain blood levels of 10 to 15 mg. (or more) per 100 cc. until the spinal fluid has been sterile for two weeks. When pocketed pus is suggested, the drug should be given until this risk has subsided. Penicillin is of paramount value and should be given intramuscularly and intrathecally in generous amounts (see general principles, above).

At the present time, the value of specific antipneumococcus serum as an adjunct to these measures is unknown. Experience may well show that some patients, particularly infants, would derive additional benefit from this therapeutic agent.

*Streptococcal Meningitis*—As mentioned in the general discussion, an attempt should be made to eradicate parameningeal infections. This is particularly true of streptococcal meningitis, which so often traces its origin to a paranasal sinus or mastoid infection.

Penicillin intramuscularly and intrathecally effects cures quite regularly, but the commoner sulfonamides require fewer lumbar punctures and other injections and in general are to be preferred. In resistant infections, penicillin may be given intrathecally along with sulfadiazine by other routes.

In the most severe infections, immunotransfusions of serum or compatible blood are of theoretical value. The organism must first be iso-

\* Courtesy of Dr. Leah Seidman.

lated and the donor whose fresh defibrinated blood exhibits optimal phagocytosis is selected

*Staphylococcal Meningitis*—Penicillin is now the drug of choice in meningitis due to the *Staphylococcus aureus*, although cures have been reported following the use of sulfonamides, particularly sulfathiazole. Large doses should be given early in the course of treatment. Abscesses should be drained.

*Meningitis Due to Escherichia Coli*—To date, all but three patients suffering from this type of meningitis at the Infants' and Children's Hospitals have died. There are reports in the literature (*Lancet*, 248 176 [Feb 10] 1945) of adults who were successfully treated with 30 gm of urea and 2 gm of sulfadiazine by mouth every four hours.

It is possible that meningitis caused by some of the other gram-negative bacilli would respond to this treatment. Transfusions of blood may be worth while.

**Conclusion**—In conclusion, one should emphasize that early recognition of meningitis is of extreme importance and time and thought spent in the first few days of treatment usually pay big dividends. One should not be discouraged by seemingly hopeless situations or slow response to treatment. Adequate citizens capable of useful and happy existence may be the reward of perseverance.

# THE TREATMENT OF COMMON ARTHRITIC CONDITIONS

FRANCIS COOLEY HALL, M.D., F.A.C.P.\*

TREATMENT of common arthritic conditions is the treatment of a variety of diseases presenting symptoms and signs in and about joints. To many, symptoms of arthralgia or arthritis seem mysterious, both as to cause and treatment, and the only way to help the patient seems to be to prescribe one of the analgesics such as salicylates. This is often done with the realization that a certain number of people have joint pains which will disappear anyway if serious damage to the articular tissues has not occurred, while the aspirin temporarily relieves the pain, but it is also given with the feeling that no one knows anything about arthritis, and nothing much can be done about it. Granting our limited knowledge, we think that most patients can be relieved and the joint disease arrested in a high percentage of cases, and this article attempts to set forth a means of approach to the problem.

Certain general statements need to be repeated again and again in order to keep a proper perspective and to avoid getting into a rut which leads to the treatment of all joint disturbances in the same way, using the latest popular therapy. (1) Joint pain may be due to one of many different conditions, and it is important to find out in each individual case what particular factors produce the joint pain. (2) A person who seeks a doctor because of joint pain is sick. It is important to start with this premise in mind and to search most diligently for the underlying causes of this ill health or subnormal state. One would then consider the joint pain as the smoke of the fire. This should result in a most careful study of the patient as a whole. (3) It follows that the whole patient should be treated in addition to the joint condition.

The patient should be studied with three objectives in mind: (1) to determine whether he has a nonarthritic condition which is part of some recognizable disease not arthritis, (2) to determine whether we are dealing with a twilight zone of arthritis—a mild form of joint pain and swelling which we speak of as arthralgia—and (3) to determine whether we are dealing with a true arthritis. Careful study should easily rule out some of the diseases frequently, carelessly diagnosed as

---

From the Second and Fourth Medical Service (Harvard) Boston City Hospital and the Department of Medicine, Harvard Medical School, and from the Robert Breck Brigham Hospital, Boston.

Junior Visiting Physician, Boston City Hospital. Instructor in Medicine, Harvard Medical School, Senior Visiting Physician, Robert Breck Brigham Hospital.



arthritis, but it is important to keep in mind others such as Paget's disease, neuritis from avitaminosis, osteomalacia, pernicious anemia with spinal cord changes, hyperparathyroidism, Parkinson's disease associated with muscle rigidity rather than tremor, carcinoma, spinal cord tumor, ruptured intervertebral disk, various conditions causing edema such as nephritis, hypoproteinemia, myxedema, scleroderma, sclerodactylia and dermatomyositis

### CLASSIFICATION

The twilight group of diseases associated with joint pains which are called "arthralgia" because we do not yet know that they represent true arthritis, might include postural joint strain, thyroid deficiency, menopausal state or ovarian deficiency, vitamin B complex deficiency, psychologic states and emotional conflicts, and physical fatigue

A convenient classification\* of cases of true arthritis follows

#### I ARTHRITIS OF KNOWN ETIOLOGY

##### A Traumatic arthritis

##### B Infectious arthritis

- 1 Associated with diseases due to known specific organisms such as the gonococcus, staphylococcus, streptococcus, pneumococcus, meningococcus, tubercle bacillus, typhoid bacillus, *Treponema pallidum*, the brucella group, *Bacillus dysenteriae*, the organism of lymphopathia venereum, etc
- 2 Associated with diseases probably infectious, such as acute disseminated lupus erythematosus, erythema nodosum, ulcerative colitis and periarteritis nodosum

##### C Metabolic arthritis, gout, scurvy, ochronosis

##### D Allergic arthritis, serum sickness

##### E Neuropathic arthritis, rabes dorsalis (Charcot's joint), syringomyelia, leprosy, yaws, hemiplegia, peripheral nerve lesions

#### II ARTHRITIS OF UNKNOWN ETIOLOGY

##### A Rheumatoid arthritis (atrophic, proliferative, or chronic infectious arthritis) This also includes Still's disease, rheumatoid spondylitis (Marie-Strümpell, von Bechterew's types) and psoriatic arthritis

##### B Degenerative joint disease (degenerative arthritis, hypertrophic arthritis, osteoarthritis, and German arthritis deformans)

##### C Rheumatic fever

#### III MISCELLANEOUS TYPES OF ARTHRITIS

Fibrositis, hemophilia, purpura, pulmonary osteoarthropathy, intermittent hydroarthrosis, hysteria

It is frequently stated that one should make the diagnosis of arthritis early, before there is clear-cut clinical or roentgenologic evidence of damage to the essential joint structures. This is a difficult thing to do, and even physicians who are spending most of their time seeing arthritic patients find it so. They would even disagree as to the nature of the disease in many early cases. It is for this reason that in early cases it is important to take the matter seriously and in taking the his-

\* Cabor, R. C. and Adams, F. D. *Physical Diagnosis* Baltimore, Williams & Wilkins Co., 1942

tory to look for some of the pathologic states and common errors of living which are found in patients with arthralgia or with true arthritis. Correcting such abnormalities will often lead to improvement of the patient's general health and to a relief of the joint pains. The abnormalities most commonly found are discussed below.

### ARTHRALGIA

**1 Joint Disturbances Due to Fatigue**—It is quite common to find as a background of joint disturbances habits of living that lead to real fatigue. Sometimes the patient is getting to bed late at night because he is unable to sleep. In such cases the cause of the sleeplessness needs to be found. Usually one finds that a person is working hard all day under pressure, sits up late at night to read or do other things, and averages six or seven hours of sleep when eight or nine hours are needed. Sometimes it is ambition that drives a person to overwork and too little sleep, sometimes it is financial necessity accompanied by worry. The result is a sapping of his physical vitality. Where such lack of sleep is found, we often prescribe twelve to sixteen hours daily in bed, and we usually prescribe this even when there is no deficiency in sleep. Helping the patient to learn what to leave out in life should be a constructive part of therapy where overwork and too little sleep are factors.

**2 Joint Pains Resulting from Emotional States**—It follows from the above that the drive of strong emotional states leading to overactivity and too little sleep can be important, but at other times one finds home conflicts which may be enormous and which may even require psychotherapy. At the moment one finds worry about sons in the war interfering with sleeping and eating.

**3 Postural Joint Strains**<sup>1</sup>—These can be important as factors in causing pain in the cervical spine, or in the lumbar and sacroiliac regions, or in the knees or feet of patients who obviously stand incorrectly. Strain alone may be present, or it may be superimposed on arthritic conditions of other origin. Where postural strains exist, they should be relieved by corrective exercises for back or feet plus in many cases back braces, foot plates, and short periods of rest throughout the day in hyperextension. Often there is some reason for the poor posture other than bad habits and ignorance—conditions which cause easy fatigability, such as too little sleep, thyroid deficiency, or some other disease.

**4 Joint Pains of Thyroid Deficiency**<sup>2</sup>—If marked, thyroid deficiency should be easily recognized but we occasionally see a patient who does not have all the characteristic symptoms and signs, but does have a low metabolism and a high blood cholesterol, and whose joint pains respond to thyroid gland therapy.

**5 Joint Disturbances Associated with Nutritional Deficiency**—The two most common findings in patients complaining of joint pains are in-

complete nutrition and the glandular imbalance of the menopause.<sup>3</sup> As we have watched patients with these conditions, we have come to the conclusion that these deficiency states lead to increased vulnerability of tissues so that the trauma of ordinary use—trauma to joint tissues and to muscles and tendons—produces pain and various degrees of disability. We became convinced of this with regard to the menopausal group by an unusual experience with one patient.

The patient, who was at the physiologic menopause, had many menopausal symptoms and was hospitalized because of the extreme pain in most of her joints. This was accompanied by hypertrophic arthritis in the fingers. However, it became quite clear that the tissues all over the body were abnormally sensitive. Pressure over the forearm would make her cringe. Taking the blood pressure caused pain. Abdominal examination was unsatisfactory and caused discomfort, and pelvic examination was impossible for the same reason. Three weeks later, following therapy with large doses of estrin, most of this sensitivity had disappeared, and all examinations could be made without distress.

We have seen instances somewhat less striking than this in many patients at the menopause. We have seen nothing as dramatic in cases of incomplete nutrition, but certain responses have suggested that incomplete nutrition may well be responsible for somewhat similar symptoms.

Many physicians apparently are unaware of the prevalence of incomplete nutrition in patients with joint disturbances. It is pointed out that most people eat a satisfactory diet. However, if one watches tongues, skin and eyes for evidence of incomplete nutrition, one finds a great many more cases of avitaminosis in patients with seemingly adequate diet than one would believe possible. We find only a few instances of an *incomplete intake* of the various protective foods. Among women the most common foods left out are milk, eggs and meat (or protein foods). This last is more common of late, and we have observed quite a number of persons with the total protein of the blood low and some edema of the ankles, which with the history of incomplete intake of protein would definitely indicate hypoproteinemia. A certain number of people have an *increased requirement* for protective foods. The requirement is definitely increased by long hours of work and short hours of sleep. It is increased by alcohol, sugar, hyperthyroidism, pregnancy, and infections.

The most common cause of incomplete nutrition, however, seems to be hyperperistalsis resulting in *incomplete absorption* of food. The most dramatic cases are seen in patients with diverticulosis or an irritable colon. They come with a history of having had three to five bowel movements a day over a long period of time, or intermittent attacks of this hyperperistalsis. Such patients usually show very definite evidence of B avitaminosis in the tongue and skin, but in all probability there is a deficiency of all known vitamins, plus a probable deficiency of other food factors that we do not yet know. Less striking, but

apparently very important, are instances of incomplete nutrition in patients who are convinced that they require a daily cathartic and who never have normal, formed bowel movements. In all such patients it is obvious that the food is not being processed and absorbed within a normal period of ninety or 120 hours, but is being hurried through the bowel as Burnett<sup>4</sup> has shown. Patients with these conditions can have the most bizarre symptoms and signs even when obese—symptoms such as are mentioned in the literature on avitaminosis.

One of our earliest cases was quite dramatic in its symptoms and response to therapy. The patient was an extraordinary 70 year old woman who until a short time previously had been running a newspaper in a small town, and had more or less "sparked" most of the town activities. She was a widow with no special ties and she decided to come to Boston to paint portraits as an avocation. Her history indicated that she had always been overscrupulous and careless about her eating. She had had intermittent gastrointestinal disturbances with diarrhea, and she had left out of her diet many important foods. Once in Boston she soon found herself too tired to do her marketing or painting. The arthritis of which she complained was not explained. One found very little except mild hypertrophic changes in certain joints and the symptoms were all out of proportion to the physical findings. There was some tenderness about the joints and a tremor of the right hand which we could not explain. Her tongue and skin showed mild signs of vitamin B deficiency. We prescribed sixteen hours in bed in twenty-four as complete a diet as possible, somewhat low in roughage but containing a large amount of protective foods such as milk, eggs and meat, of which she had been eating but little. We gave her large amounts of vitamin B, covering the other vitamins by diet, and several times a week gave her an injection of "vitamin B complex parenteral." In one month most of her symptoms had entirely disappeared and in the last five years she has remained well by following a proper diet and taking supplementary vitamins.

One wonders whether such a state can lead to true arthritis, we have cases which seem to indicate that it can do so.

An example is a doctor's wife, now over seventy who had been having arthritis in the knees and hips for some years before she was seen five years ago. She was found to have diverticulosis, but because of her love of salads, cole slaw and other green vegetables and fruits she persisted in eating such foods, and for years she had had considerable gastrointestinal difficulty with frequent periods of diarrhea always with a great deal of flatulence and always or three soft bowel movements a day. When seen, she had a tongue typical of B avitaminosis with ulcerations thought to be due to lack of nicotinic acid or riboflavin. Her skin was somewhat dry. At the worst she had to live a very restricted life because of the joint pains which at one time involved the fingers, wrists and other joints in a transitory fashion causing marked hypertrophic changes in the hips and knees and marked limitation of motion. She was unable to take vitamins by mouth without increasing the gastrointestinal symptoms. For several years, therefore, she has had two or three injections a week of liver or vitamin B complex. The result is that her arthritis, which appeared to be of the mixed type, has been less and less conspicuous, and her activities are consistent with those of a woman of seventy-three.

It seems to be important in such cases to reeducate the patients with regard to diet and bowel habits. One has to point out the necessity of

thinking of the gastrointestinal tract as a factory for the processing and absorption of food, and one must encourage the patient to have only one formed movement every day or every other day. Often it is quite a psychological hurdle to convince such patients that dire things will not happen if the bowels are kept really slow acting. One has to plan the diet so that there will be a proper amount of green vegetables and fruit in a form that can be tolerated. Such patients often have to give up indefinitely raw vegetables such as salads and celery, and rough foods like corn and sometimes spinach. Bismuth or kaolin and paregoric, to be taken before going to bed each night, may be of value at times, when only mild soothing of the bowel is needed. Sedatives sometimes help such hyperperistalsis. The presence of hyperthyroidism needs to be ruled out, and emotional conflicts resolved, if present. Supplementary vitamins of all types would seem to be indicated in very large doses. Until one is convinced that absorption is complete, especially in older persons, parenteral therapy is often indicated. In such cases we give very large doses of vitamins by mouth, using the multiple vitamin preparations and 2 cc of B complex with a liver base intramuscularly twice a week. As these persons are sick, it is important to treat them as such, with extra quotas of rest which of course cut down the nutritional requirements.

6 Menopausal Arthralgia<sup>8</sup>—This type of joint pain should be easily recognized if sought. The diagnosis is clear when the arthritis occurs within weeks or a few years after destruction or removal of the ovaries, and when definite symptoms of the menopause are present. It is usually possible to detect this type of arthralgia when it occurs at the physiologic menopause. It may be easily overlooked when other contributing factors to the patient's poor health are present, such as those previously mentioned. It is apt to be out of mind entirely when it occurs superimposed on a definite type of arthritis such as the hypertrophic type or the rheumatoid type. Its importance sometimes in such conditions cannot be overstated.

An example of this occurred in a nurse of 56 who came to the hospital severely crippled with rheumatoid arthritis of ten years' duration. In addition to the permanent joint changes there was marked pain in the left hip requiring her to be put into a plaster shell. Improvement seemed to stop after a few weeks, and the whole history was again searched for leads suggesting some specific etiology. Though she had denied any menopausal symptoms, we had suspected that her sleeplessness, her depression and nervous tension, and her dissatisfaction with the temperature of the room at night, however we kept it, represented menopausal symptoms. Further questioning brought out other symptoms, especially mental depression. The use of estrin produced an almost complete personality change in the patient and started her toward improvement. Instead of being bedfast in the last few years she has become increasingly active, and though we do not attribute this to the sex hormone alone, we feel that it contributed to her improvement in no small measure because improvement in the joints as well as in her general health occurred within a few weeks after she took this material.

We still do not know whether this glandular readjustment of the menopause, or estrin deficiency, can in itself cause joint changes that we term arthritis. As one watches patients with arthralgia alone, those with arthralgia plus tissue changes in a few joints, and finally those with arthralgia plus a good deal of arthritis, one cannot but note what appears to be a transition from mild to severe cases. Intensity and duration of the condition seem to influence the joint tissues in producing the clinical picture found. One wonders then whether estrin deficiency or the glandular imbalance of the menopause may not play a major role in some cases developing into true arthritis. One could set up an hypothesis that (1) the tissues are made more vulnerable by ovarian deficiency to the trauma of ordinary use and the continued trauma results in chronic inflammation and the changes we think of as hypertrophic arthritis. Other possible effects of sex hormone or lack of it are suggested by the work of Weisberger,<sup>6</sup> who demonstrated that (2) in certain women who have B avitaminosis large doses of vitamin B will not change the tongue and skin toward normal until estrin has been added. There is, furthermore, increasing evidence that (3) castration in laboratory animals may increase susceptibility to infection, while fortification by estrin may increase resistance, as shown by Aycock<sup>6</sup> and others. We believe we have observed these principles exemplified in patients with arthritis. Lest the diagnosis of infectious arthritis or of rheumatoid arthritis be too easily made in patients at the menopause because of the presence of an elevated blood sedimentation rate, it is important to state that elevated rates are the rule in castrates with menopausal symptoms, but without joint pains.<sup>7</sup>

For estrin therapy we favor giving the amount that will eventually produce swelling or tenderness of the breasts, pelvic symptoms such as those manifested at menstruation, or mild leukorrhea. The patient's cooperation in reporting these symptoms must of course be obtained. These large doses are necessary to make certain that enough estrin is given. Once a saturation of tissues occurs, smaller maintenance doses are required, and these should be just enough to prevent breast and pelvic symptoms. Treatment should be stopped for a week or ten days every six weeks. We use doses of 10 000 rat units three times a week to 2000 rat units one to three times a week, depending on the severity of the symptoms. The intramuscular route is preferred until the symptoms are under control, when one substitutes oral medication using 0.5 mg. of progynon D-H tablets two to three times a day, or 0.5 to 1.0 mg. of enteric-coated stilbestrol tablets once a day at bedtime. Again, we favor stopping this course of therapy every six weeks for a period of at least one week. Starting with an oral preparation which may be very insufficient, or which like stilbestrol may upset the gastrointestinal tract, has not been successful with us, for one of the things that the patient needs in the first six or eight weeks of treatment is the evidence that she is better, and if medication is given that upsets her

or if improvement is so slow as to be unconvincing, she is likely to lose confidence in the whole program

Not infrequently there is evidence of incomplete nutrition as well as a menopausal problem in a patient, and one cannot help but speculate as to whether patients with severe menopausal symptoms and those with symptoms that continue for many years may not lack certain chemical building stones necessary for the glandular readjustment. It would seem basically important in such patients to make sure that any nutritional deficiency is corrected. Surely the menopause should be a relatively normal stage of life and not attended by as much difficulty as we often see. It is our impression that the patients who receive supplementary vitamins as indicated make the best response and require estrin treatment for a shorter length of time than when vitamins are not used, and we suspect that some of these patients might do well with simply the nutritional approach alone.

#### THE ARTHRITIDES

Much of what we have noted in respect to arthralgia applies equally to arthritis, for the various conditions we have mentioned are commonly found in persons with chronic arthritis, but one of the first important things to do in studying a patient is to determine if possible the type of arthritis with which one is dealing, to the end that where the cause is known, the treatment may be precise. Traumatic arthritis is usually clear-cut and the chronic microtrauma of poor posture is usually easily recognizable. Sometimes only trauma is present. It is a contributing factor in practically all other types of arthritis. The possibility of the arthritis being due to infection will naturally be kept in mind and, so far as possible, infection will be treated specifically by modern drugs or removed surgically. Space does not permit the inclusion in this article of a discussion of gout or allergic arthritis or the neuropathic group.

It is especially in the two main types of chronic arthritis, namely rheumatoid and hypertrophic arthritis (or degenerative joint disease), that what we have noted in the preceding paragraphs seems to apply. We still do not know the cause of these two types of arthritis. The rheumatoid type is still generally thought to be due to infection, while degenerative joint disease, or hypertrophic arthritis, is thought to be due to the wearing out of the joints. Descriptions of the clinical pattern and the pathological findings in these two types can be found in textbooks. The fact that there are so many mixed types raises again the old question as to whether both types may not have common factors in their etiology, with the character and intensity of the irritant, its duration, plus the presence and absence of the trauma of use resulting in the pathological findings which we use to distinguish the two types of joint disease. Joint tissues can respond to various irritants or traumas in only a limited number of ways, and one could offer con-

siderable support for this theory. Granting that the rheumatoid type seems to be most closely allied to known infectious processes in joints, and that it responds in a considerable number of cases to gold salts therapy which is thought to act directly or indirectly on an infectious process, still one cannot help wondering why one patient throws off infection easily while another seems to have no resistance to such infection. One must conclude that the treatment of the whole patient and the elimination of all contributing factors are important in both types, even if infection should be proved to be the cause of rheumatoid arthritis.

**Rheumatoid Arthritis**—Serious treatment of the patient as a whole is especially important in rheumatoid arthritis. Occasionally one sees a case in which infection seems clearly to be responsible for the arthritis, but usually there is no such history. Much more commonly one finds a history of depletion with overwork, too little sleep, poor eating habits, worry, loss of weight, continued mechanical irritation of already damaged joints with the help of "pain-killers," and a cathartic habit until disability is fairly complete. Treatment in such cases, if results are to be permanent, requires a maximum of rest so that the patient obtains at least sixteen hours a day in bed, even in early cases, and in addition the best possible diet and one calculated to keep the bowels slow-acting. Supplementary vitamins are given in large doses, especially if there is evidence by skin and tongue of incomplete nutrition—a common finding. Enough aspirin is prescribed to provide rest. It is important to keep the muscles, the circulation, and the nervous system in good condition by exercises for the trunk, with a little motion for the involved joints. Use of the weight-bearing joints may have to be discontinued for a while, however, for sore knees or hips will not improve, if badly irritated, as long as weight bearing continues. Heat to the involved joints two or three times a day gives considerable comfort in the early or mild cases, especially where there has been an obviously marked fatigue or deficiency.

The measures outlined will in most cases lead to improved health, which is soon followed by improvement in the joints. Unfortunately, some patients will not improve under such a program alone, and in these cases one must consider the risk of gold salts therapy. If the liver and kidney functions are normal, and there is no marked avitaminosis, the risk of giving gold salts is probably less than the risk of withholding it. However, we have become very conservative in its use as we still have numerous patients in whom gold salts therapy has had to be stopped because of skin itching, irritation of the kidneys, or the development of anemia or a low blood platelet count. We have seen patients who were greatly benefited by one course of therapy but whose arthritis recurred. In most of these the further use of gold salts was contraindicated, in others it proved to be of little value. Inasmuch as the infectious origin of some rheumatoid cases is in doubt and since



many cases given this diagnosis present contradictory pictures one wonders whether other types of arthritis might not be included in this classification. In the circumstances it seems important in an individual case to have an open mind and feel one's way along, doing everything possible to build up the general health of the patient, and not relying on any one drug.

We have used gold therapy in perhaps 150 cases of rheumatoid arthritis. We are not enthusiastic about its value when it is used alone, and we still are afraid of gold, but we could point to numerous cases that did not respond to treatment until gold was used, and that appeared to be completely arrested following its employment. In using gold salts we generally give 10 mg. of a product such as solganol-B in oil from two to four doses at intervals of four to five days, then two to four doses of 25 mg. at weekly intervals, then maximum doses of 50 mg. once a week. We have continued this program until the patient's symptoms were markedly lessened, or until a total of 1 gm. of the salt has been given. If the patient's symptoms are greatly improved at any point in the treatment we increase the interval between doses to two, three or four weeks. Even when the arthritis seems to be under good control, we continue to give 50 to 100 mg. once a month for six months more.

We are conscious that the doses advised are smaller than those ordinarily used. Our results are probably less spectacular, therefore, than those of many others who report on the use of gold salts. It should be stated, however, that even with these smaller doses we have seen enough patients with prolonged and disfiguring dermatitis, with prolonged periods of albuminuria, or with falls of blood platelets below 200,000 per cc. to make us eager to avoid the more frequent toxic reactions that all agree can result from the larger doses. We prefer, first, to use every other means possible to help our rheumatoid arthritic patients, then if these means fail to use as little gold as possible, and finally if gold is used to stop it as soon as possible.

During the process of treatment it is particularly important to educate the patient in the art of living, and then to keep in touch with him after he is considered to be well. Crippled joints can be reconstructed to an extraordinary extent by the orthopedic surgeons, and where it is perfectly clear that the arthritic process is quiescent as noted by the absence of any new joint disturbance, the absence of morning stiffness, and the absence of an elevated sedimentation index, one can expect operative procedures on joints to be remedial without the development of stiff joints from the operation.

**Degenerative Joint Disease and Hypertrophic Arthritis (Osteoarthritis)**  
—Trauma is considered to be the major factor in the development of hypertrophic arthritis. Trauma is unquestionably an important factor in all joint diseases and needs to be so considered, yet careful studies of patients seem to indicate that an  $x$  factor must be added to the

trauma. A large number of women develop hypertrophic changes in the fingers at the menopause, which suggests that the menopause can be one of those  $x$  factors. Incomplete nutrition may be another such factor. Certainly most students of hypertrophic arthritis do not believe that infection plays a role. If there is an  $x$  factor present, they believe it must be of metabolic origin. In some cases thyroid deficiency seems to be responsible.

The presence of hypertrophic arthritis is apt to be minimized by physicians, and patients are told that the disease will never cripple them and that not much can be done about it, anyway. We do not agree that nothing can be done. In menopausal cases we have seen hypertrophic nodes on the fingers become actually smaller, as measured by jewelers' rings, when the patient was given adequate estrin therapy. We have seen patients with marked hypertrophic changes in the spine or knees lose the pains, which were presumably due to these hypertrophic changes, when trauma was removed and proper nutrition given. It does not seem to us that the hypertrophic lesions seen by  $x$ -ray plays any convincing part in the causation of pain unless the changes are excessive. One sees marked arthritic changes in the spine, for instance with a history of no pain, and on the other hand, considerable pain may be present but little change is seen by  $x$ -ray. The cause of the pain may be one of the factors already mentioned, such as estrin deficiency, nutritional deficiency, or even infection plus trauma. In addition there may be a history of marked fatigue, postural joint strain, obesity from overeating of the wrong foods with under-eating of the protective foods.

When the knees or hips are involved, the disease cannot be treated lightly. Normal use of already damaged weight-bearing joints will aggravate the damage as the years pass. A once damaged joint will degenerate more rapidly than one not damaged. In addition to the general measures the cardinal principle of treatment is to keep the patient off his feet when there is pain in the hip or knee. Though cartilage is known to have little power of repair, the inflammatory changes in the other joint structures may often be arrested as indicated in the following example.

A patient, now 70 years old was seen fifteen years ago for the first time. She came to the office in a wheel chair pushed by her husband and she moved on crutches. She had had involvement of the right hip for at least five years. She had been overweight and had eaten an adequate diet. The condition appeared to have started at the menopause, but she was well past that event. She had less than 50 per cent of normal motion in the right hip. The motion was painful and the  $x$  ray showed a flattened head of the femur with obliteration of the joint space. She was a very cooperative patient and wished to do everything possible to get well. Ordinarily in five years such a patient walks with a great limp still has a great deal of pain, and the disability has markedly increased. For some years now she has used neither crutches nor cane, and rarely has pain in the hip. While she was given various types of medication, we believe that

her improvement was due to the fact that she was willing over a long period of time to go to bed whenever she had pain, and to stay there until the pain passed. At first she was in bed a great many weeks. As the years passed, she would occasionally have to go to bed for only a few days at a time. She had learned that her damaged hip, if used beyond a certain point, would always give pain, but she had become very alert to recognizing stiffness after sitting as the first evidence of increased joint irritation. She would then spend a few days in bed, and would be able to be active with restrictions for some weeks before having to do the same thing again.

Patients without the marked disability present in this patient will often recover almost normal walking capacity under such a program, because the reserves of the joint seem to be as great as the reserves in other organs and a patient can be fairly active in spite of a good deal of joint damage. This attitude is similar to that taken in heart disease, in which the patient has to build up his cardiac reserve and then learn to live within it. We have other patients who had had similar records. Some have taken thyroid or estrin, others have needed to watch their diet or their bowels carefully and take supplementary vitamins, but they all have kept off their feet when there was pain or stiffness. Patients with hypertrophic arthritis often tend to be overweight while those with rheumatoid arthritis tend to be underweight. It seems important to put weight onto the latter and to take weight off of the former. However, we are convinced that the removal of weight by dieting must be done slowly, carefully, and with great stress on protective foods and supplementary vitamins. The removal of weight seems to help definitely the nutrition in joints and it also serves to remove in part the trauma that overweight puts onto already damaged weight-bearing joints. Thus again stress needs to be laid on treating the patient's general condition as well as his joints.

Although many cases of arthritis will respond to the therapeutic program which has been outlined, not all will do so. We cannot reverse the process and expect to regain a normal joint in any case in which definite damage has been done. In such instances the patient has to learn to live within his limitations, although those limitations may be lessened by the orthopedic surgeon. We do believe that this multi-angled and varied approach to the treatment of joint diseases gives us fewer failures than we have had in the past.

#### BIBLIOGRAPHY

- 1 Hall, F. C. Observations of a Medical Man in an Orthopedic Clinic. *Boston Med & Surg J.*, 194 432-440 (Mar 11) 1926
- 2 Hall, F. C. The Importance of Mechanical Trauma in Joint Pain. *M CLIN NORTH AMERICA*, 18(4) 935 (Jan) 1935
- 3 Hall, F. C. and Monroe, R. T. Thyroid Gland Deficiency in Chronic Arthritis. *J Lab & Clin Med.*, 18 439-457 (Feb) 1933
- 3 Hall, F. C. The Value of Estrogenic Substance in "Menopausal Arthritis". *Medical Papers (Dedicated to Henry Asbury Christian)* Baltimore, Waverly Press, Feb 17, 1936, pp 928-935

- Hall, F. C. Menopause Arthralgia. *New England J. Med.*, 219 1015-1026 (Dec. 29) 1938
4. Burnett, F. L. Fecal Units and Intestinal Rate, a Basis for the Study of Health and Intestinal Indigestion. *Boston Med & Surg J.*, 184 371, 415 (April 14 21) 1921
- Arthritis, Anabolic Nutrition and Health. *Am. J. Med. Sc.*, 188-93 (July) 1934
- Variations of Intestinal Rate. *J.A.M.A.*, 85 1777 (Dec 5) 1925
- Intestinal Rate, Normal Nutrition and Health. *Medical Papers* (Dedicated to Henry Asbury Christian) Baltimore, Waverly Press, Feb 17 1936 pp 683-693
5. Weisberger D. Deficiency Diseases of the Oral Cavity. *Massachusetts Medical Society Annual Meeting* May 7, 1942
6. Aycock, W. L. A Subclinical Endocrinopathy as a Factor in Autarceologic Susceptibility to Poliomyelitis. *Endocrinology* 27(1) 49-57 (July) 1940
- Foley G. E. and Aycock, W. L. The Effect of Stilbestrol on Experimental and Streptococcal Infection of Mice. *Endocrinology* 31 139-145 (Sept.) 1944
7. Unpublished studies made by the author in 1940 at the Women's Free Hospital, Brookline, Mass., in conjunction with Dr. Burton E. Hamilton, Dr. George P. Sturgis and Dr. George P. Whitelaw

# SURGICAL INDICATIONS AND TREATMENT OF PRIMARY CANCER OF LUNG, BRONCHIECTASIS AND LUNG ABSCESS

JOHN W STRIEDER, M D \*

## PRIMARY CARCINOMA OF THE LUNG

THE increasing frequency with which cancer of the lung has been reported as a cause of death in recent years has aroused considerable speculation whether the increase represents a real change in the incidence of this form of malignant neoplasm or is merely the result of improved methods of diagnosis in combination with a more careful search for a disease that has attracted attention because it is reported more frequently than it has been in the past. Dorn states that between 1914 and 1930 the death rate from cancer of the lungs and pleura increased by nearly 400 per cent, as compared with an increase of 20 per cent for all forms of cancer combined. Slightly more than 8000 new cases of primary cancer of the lung are diagnosed and receive treatment for the first time each year. Recently it has been shown that the lung ranks second only to the stomach as the primary site of cancer.

Any male patient of middle age or beyond, who develops cough and expectoration, with or without hemoptysis or blood-streaking, and who cannot be shown to have tubercle bacilli in the sputum, should be considered to have bronchogenic carcinoma until it is proved unequivocally that there is some other reason for his symptoms.

**Diagnostic Procedures—Roentgenography**—The first step leading to diagnosis is a roentgenogram of the chest. In most cases, this simple procedure suggests the diagnosis either by indirect evidence, such as atelectasis of a lobe or lobes due to an obstructive bronchial lesion, or by the more positive evidence of an infiltrative hilar lesion or parenchymal tumor. Alexander states that despite the prevailing impression, most circumscribed intrathoracic neoplasms are intrapulmonary and malignant. All pulmonary abscesses and suppurative lesions should be considered as resulting from bronchogenic carcinoma. In general, one may say that the roentgenogram shows the tumor, which may be relatively tiny, less frequently than its result, which usually predominates in the clinical picture. In rare instances, the roentgenogram is negative.

**Bronchoscopy**—The second step by which a positive diagnosis can best be made before operation is almost always bronchoscopy. Various

---

\* Assistant Professor of Thoracic Surgery, Boston University School of Medicine, Boston, Massachusetts, Visiting Surgeon in Charge of Thoracic Surgery, Massachusetts Memorial and Boston City Hospitals

authors have stated that a positive diagnosis by bronchoscopic biopsy can be made in from 60 to 75 per cent of cases. If one takes into account the indirect bronchoscopic evidence of fixation, broadening of the carina or bronchial deformity, a presumptive diagnosis may be made in as high as 85 per cent of cases.

*Aspiration Biopsy*—The introduction of a needle directly into the tumor under fluoroscopic guidance, for the purpose of obtaining a plug of tissue for biopsy, has been advocated by some clinics. In my opinion, this procedure is useful in a limited number of peripheral tumors. It is not, however, entirely without hazard since deaths from air embolus have been reported. It has also been objected to on the theoretical grounds of secondary seeding of the needle track with cancer cells. There is, also, always the possibility of pleural contamination should the area needled be infected.

*Examination of Pleural Fluid for Tumor Cells (Mandelbaum Test)*—Whenever there is a pleural effusion, it should be completely aspirated and the entire amount centrifuged. The resulting sediment is fixed and examined for tumor cells. If tumor cells are found, the case is inoperable. If the fluid is bloody, it usually means invasion of the visceral and parietal pleura by the growth and also denotes inoperability.

*Exploratory Thoracotomy*—The problem of what advice to give in the 25 per cent of cases without a positive diagnosis is an important one. In Graham's opinion, the answer is generally fairly simple. If there is a reasonable suspicion of carcinoma, an exploratory thoracotomy should be performed without delay, for in this way many lives can be saved. Too often the advice of the physician has been to wait to see if anything happens. Nothing is gained by this delay, and the usual result is another victim.

*Treatment*—It is now generally recognized that the ideal in the treatment of primary cancer of the lung is its surgical extirpation by total pneumonectomy. In rare cases, lobectomy may be used, but, as in cancer surgery in general, only by the sacrifice of the entire organ can one hope to achieve the greatest number of cures.

To my knowledge, there has never been an authenticated case of bronchogenic cancer that has been reported as a five-year cure as the result of radiation therapy. It has a limited sphere of usefulness as a palliative measure and may be used in certain inoperable cases.

An analysis of the risks involved in total pneumonectomy reveals an encouraging trend for an operation that must be considered to be technically still in its developmental stage. It is of interest that the mortality figures in three widely separated clinics are strikingly similar. Graham reports three deaths in his last twenty-five cases, a mortality of 12 per cent, and Rienhoff states that in a series of twenty-three cases he had three deaths, a mortality of 13 per cent. In our last twenty-three cases at the Massachusetts Memorial and Boston City Hospitals

we have had two deaths, a mortality of 9 per cent. Such figures are reasonable ones, and should bring home the fact to the medical profession that the operation of total pneumonectomy for primary cancer does not carry with it an enormous operative risk. It has been generally believed. It should be remembered that with this operation the risk is 100 per cent.

The question of the age of the patient frequently enters into consideration of operability. At the present time, there would appear to be no empirical age limit. The general condition, and particularly the condition of the cardiovascular apparatus is more important than the chronological age.

*Inoperability*—From an analysis of current statistics and my experience, only 10 to 25 per cent of cases of bronchogenic carcinoma are operable when first considered for surgery, a sad reflection on the ability of physicians to recognize this relatively frequent disease in its early and favorable states.

The reasons for inoperability, which, as a corollary, mean late diagnosis and advanced disease, are based on certain findings. These findings have been summarized by Graham as follows:

1 *The presence of bloody fluid* This usually means invasion of the visceral and parietal pleura by the growth. In most cases, the presence of clear effusions also means inoperability; and the finding of malignant cells in such effusions makes it certain.

2 *Paralysis of the corresponding half of the diaphragm, as determined by fluoroscopic examination* This usually is due to invasion of the phrenic nerve.

3 *Paralysis of the left vocal cord in cases of left-sided bronchogenic carcinoma* This usually denotes invasion of the left recurrent laryngeal nerve as it passes under the arch of the aorta.

4 *Severe pain in the thoracic wall or down the arm* This is usually a sign and generally is evidence of involvement of intercostal nerves or of the brachial plexus. The presence of a moderate amount of pain, however, should not preclude an exploratory operation.

5 *Bronchogenic evidence of extension of the tumor into the trachea* This usually contraindicates pneumonectomy, although occasionally it is possible to remove even a part of the wall of the trachea.

6 *The presence of distant metastases* In exceptional cases, it may be justifiable to remove both the lung and a solitary metastasis.

#### BRONCHIECTASIS

In a recent paper, Riggins concludes, "The morbidity and mortality of untreated and medically treated bronchiectasis is such that the physician who routinely advises young adults with operable bronchiectasis against surgery is assuming a grave responsibility and his probability renders his patient a great disservice."

That bronchiectasis is a surgical disease and that most patients

whom it is discovered should be considered for lobectomy or pneumonectomy is corroborated in a study presented by Perry and King. Basing their conclusions on a follow-up of 400 patients, these authors show that in a twelve-year study the mortality in the nonsurgically treated cases was 26 per cent, 41 per cent of these patients dying within five years of onset and 15 per cent living twenty years or longer after onset. Of the patients who died, 78 per cent died directly from their disease. Some statistical evidence supports the view that patients who develop bronchiectasis before the age of ten do not live beyond the age of forty. Thus, of persons with the onset in the first decade only 9 per cent were living at the age of forty or over. Of the fifty-nine patients who reached the age of forty or over, in only 15 per cent was the onset in the first decade. The operative mortality in 122 modern type lobectomies performed on 116 patients was 3 per cent. The working and living capacity of the traced living patients was considered to be excellent in 67 per cent of the surgical group and in 38 per cent of the nonsurgical group.

The nonsurgical treatment of bronchiectasis is only palliative and because of the low operative mortality rate, simple lobectomy should be advised without hesitation. Even with bilateral disease the risk in bilateral lobectomy—of course in two stages—is frequently not too great. Children stand thoracic operations exceptionally well, and lobectomy early in life is almost certain to obviate the hazards of bronchiectasis that such children must face if they grow to adolescence or adult life with nonsurgical treatment.

**Diagnostic Procedures.**—1 *Bronchoscopy*—All patients suspected of having bronchiectasis should have bronchoscopy performed during the course of the work-up. Bronchiectasis is notoriously secondary to tumors, strictures and foreign bodies and frequently the true situation is revealed only during the course of the bronchoscopic examination. Moreover, the localization of the disease by the bronchoscopic visualization of the lobar or segmental bronchi from which purulent secretions are draining is of great value in determining operability and planning the surgical program.

2 *Bronchography*—The only certain procedure by which a diagnosis of bronchiectasis may be made, and its extent determined, is by the introduction of iodized oil into the tracheobronchial tree and the making of bronchograms. Before any surgical program can be planned, indeed before it can be determined if surgery is indicated, good bronchograms must be made. There are several technics by which iodized oil is introduced in bronchography. These include the intratracheal, transtracheal and supraglottic methods, all of which are in common use in various clinics today and good bronchograms may be obtained by the operator experienced with any of them. Because of its simplicity the intratracheal catheter is used in my clinics, but the primary desideratum is the adequate filling of all five lobes of the lungs. Many



of the early disappointing results in the surgery of bronchiectasis are directly attributable to undertaking surgery on the basis of poor or inadequate bronchograms

The procedure is painless, although, at times, arduous for both the patient and the operator, but it must be persevered in to achieve the desired result. It does not require hospitalization. Not infrequently two or more sittings are necessary before complete and satisfactory bronchograms are obtained.

**Treatment—Surgical**—Operation should not be undertaken on febrile patients who are in the acute or subacute phases of a pneumonitis which frequently complicates bronchiectasis and often is the incident which first leads to the diagnosis. Nor should afebrile patients, who have copious foul sputum, be considered for immediate operation. Bitter experience in the early days of this type of surgery has demonstrated that disaster follows such misguided efforts because of the complications of infection of pleura, mediastinum or chest wall due to the presence of virulent anaerobic organisms in this phase of the disease. These patients should be prepared for surgery, as will be discussed below under nonsurgical treatment.

Assuming the patient to be under 35 to 45 years of age, and otherwise presenting no serious contraindications in so far as his general condition is concerned, the indications for and types of operation may be considered under the following headings:

1 *Unilobar disease* Bronchiectasis localized to one lobe or a segment of a lobe is the ideal indication for surgery. In this situation, lobectomy or partial lobectomy (segmental pneumonectomy) may be recommended with the expectation that the operative mortality will be less than 3 per cent, and the chances for complete cure close to 100 per cent. As has been suggested by the foregoing, disease localized to a definite anatomical segment of a lobe, as the lingula of the left upper or the dorsal or basal divisions of the lower lobes, may be treated by partial lobectomy, thus conserving normal pulmonary tissue.

2 *Multilobar disease* (a) *Unilateral* If bronchiectasis is found in more than one lobe of the same lung in such combinations as the right middle and lower lobes, or the left lower and lingula of the left upper, double lobectomy or lobectomy and lingulectomy may be undertaken with little more risk than for single lobectomy. If all lobes of a lung are involved, total pneumonectomy may be offered. Here again, the risk of operation is perfectly respectable—certainly no more than 10 per cent and probably less than 5 per cent.

(b) *Bilateral* Bilateral lobectomy, in stages, is frequently performed for bronchiectasis. It is now considered routinely in planning the surgical program of suitable bilateral cases. Such combinations as both lower lobes, right middle and left lower lobes, right lower lobe and lingula of left upper lobe, or right lower and middle and left lower lobes have been repeatedly successfully treated by lobectomy in staged

operations. Even four-lobe disease (right middle and lower and left lower and lingula) has been, occasionally, successfully treated by excision. As might be expected, however, bilateral lobectomy is associated with considerably higher mortality since it subjects the patient to two major operations after the first of which he must convalesce with disease remaining in one or more lobes.

*Non-surgical*—Although surgery is the treatment of choice in bronchiectasis, much can be done to palliate the distressing symptoms of the disease in patients who, because of age, general condition or other serious contraindications, must be denied the benefit of lobectomy or pneumonectomy. Some of these therapeutic measures are also of great value, as mentioned above, in preparing patients for surgery, when it must be postponed because of the excessive amount and foul character of the sputum, or because there has been an acute exacerbation of the pneumonitis that so frequently complicates bronchiectasis. In this category, lie postural drainage, bronchoscopy and penicillin inhalation.

1 *Postural drainage* is probably the most important single adjunct in the preoperative or palliative treatment of bronchiectasis. It may be carried out continuously or intermittently as indicated under Lung Abscess. To be effectual, it must be dependent in the sense that the mouth must be lower than the portion of the bronchial tree to be drained. This may be accomplished by hanging over the side of the bed or a table, or, if it is to be continuous, when the patient is confined to bed, the foot of the bed may be elevated. For ambulatory patients, it should be practiced in the morning on arising, before each meal and at bedtime. Faithfully carried out, it will usually result in a reduction of the amount and fetid character of the sputum.

2 *Bronchoscopy* The bronchoscopic aspiration of secretions at weekly intervals for a series of five or more treatments will frequently reduce, temporarily, the amount of the sputum and render it less foul. While in no sense curative, it is often distinctly beneficial to the inoperable patient, and is an aid in the preoperative preparation of patients, when surgery must be delayed because of copious foul sputum and/or a febrile state.

3 *Penicillin inhalations* While the inhalation of finely nebulized penicillin vapor is of too recent institution to be judged critically in a sufficiently large number of cases to be of statistical significance, there is evidence to suggest its value preoperatively and postoperatively and in cases of complicating pneumonitis. Inhaled from a special nebulizer in amounts of 20,000 to 50,000 units every three hours, we have observed that the sputum will lose its foul character within a few days to a week in the few cases with which we have had personal experience.

4 *X-ray therapy* has been advocated as a method of controlling the amount of sputum in inoperable patients. Our experience with this

form of therapy has been limited, but while we have observed temporary improvement in a few cases, there has always been recurrence. Riggins has pointed out the hazard of fibrosis and chronic indurative pneumonitis inherent in this method of treatment. We believe it has little to recommend it, and much to condemn it

### LUNG ABSCESS

Lung abscess is a common disease but until the middle 1930's it was largely considered to be a medical problem, and the mortality ranged as high as 60 per cent, as reported by various clinics. While it is true that infected emboli lodging in the pulmonary circulation may result in abscess formation, it is now generally accepted that the typical putrid lung abscess is the result of the *aspiration* of the *proper* sorts of infected material. Thus, while the introduction of the ordinary pyogens into the bronchus of a dog will have no effect, the introduction of the scrapings from pyorrhea pockets from the human mouth containing a mixed flora of anaerobes, will result in the formation of putrid lung abscess with a high degree of frequency. Although perhaps 20 per cent of lung abscesses will result in spontaneous cures, the disease is now generally regarded to be primarily of surgical potential and should be so regarded from its inception.

**Diagnostic Procedures—Sputum Examination**—As in every instance of pulmonary disease in which there is sputum, this important secretion should be subjected to repeated examinations of concentrated pooled specimens for tubercle bacilli. Foul sputum may occur in rare cases of chronic cavernous pulmonary tuberculosis. On the other hand, occasional acid fast organisms may be present in the purulent secretions of a lung abscess, but it has been pointed out that this may represent sequestration of old healed foci of tuberculosis that chance to be in the field of pulmonary suppuration. Consequently, the findings of a few acid-fast bacilli once or twice in a series of examinations, while adding to the complexity of the problem, does not necessarily mean that the situation which must be met is not that of true lung abscess. It does mean, however, that the physician must be doubly alert in evaluating the evidence. A wide variety of other organisms, including most of the common mouth flora, is invariably present in the sputum. The anaerobic streptococcus is a constant finding and spirochetes and fusiform bacilli can usually be demonstrated in freshly collected specimens. Elastic fibers may be present indicating tissue destruction, but they are also present in the sputum arising from ulcerative lesions of the larynx and trachea.

**Roentgenography**—One of the most important diagnostic aids in lung abscess is the roentgenogram. By this means, the demonstration of a cavity with a fluid level in the apex of the lower lobe is of prime significance. For purposes of localization, therefore, exposures should

be made in the anteroposterior and lateral positions. Such a finding, with a surrounding zone of increased density, in the absence of tubercle bacilli in sputum which is foul, is strong presumptive evidence, although cysts, encapsulated empyema and certain bronchogenic cancers with necrotic centers may cast shadows indistinguishable from that of abscess. The technic of making the anteroposterior exposure with the patient reclining with the affected side uppermost, often serves to confirm the presence of a fluid level by making its direction parallel to the long axis of the body. Taking the roentgenograms early in the morning, before the patient has had an opportunity completely to evacuate the contents of the abscess cavity, is another method whereby fluid levels may be demonstrated.

As a matter of fact, only in about 50 per cent of cases can one demonstrate a cavity and a fluid level, which combination depends upon a patent communicating bronchus or, at least, air and pus in the cavity. In many instances, the cavity is filled with sequestrum or debris, or is obscured by the dense surrounding pneumonitis. Under these circumstances, recourse may be had to a series of laminograms to demonstrate the suspected cavitation.

During the early acute stage, a cavity may not be demonstrable since the process is essentially a pneumonic area which it resembles in the roentgenogram. Actually, the modern concept of the disease, which renders earlier drainage imperative, frequently leads to operation without positive roentgenographic evidence of cavitation.

On the not infrequent occasions when the abscess cavity is located in the apex of the lung, it may be differentiated from tuberculosis with great difficulty, although in these circumstances the physical signs of tuberculosis and the assiduous examination of the sputum for tubercle bacilli usually will aid in the differential diagnosis.

*Bronchoscopy*—Every case of lung abscess without exception must be examined bronchoscopically in order to rule out an obstructing neoplasm, stricture or foreign body as the cause of the abscess. The bronchoscopic examination also serves as a valuable localizing maneuver, since the bronchoscopist who should, preferably, be the thoracic surgeon, is frequently able to observe pus exuding from a particular bronchus which drains the suspected bronchopulmonary segment. While the older concept of drainage of a lung abscess bronchoscopically is now realized to be impossible of accomplishment, the bronchoscopist may temporarily improve drainage by shrinking down the swollen mucosal surfaces or actually removing obstructing granulations. Secretions may also be obtained directly from the bronchus for bacteriological study.

*Bronchography*—With the exception of the demonstration of a blocked bronchus leading to the suspected area, the introduction of iodized oil into the bronchial tree has been, in my clinics, of little definitive value in the diagnosis of lung abscess. If the abscess is acute,

oil will rarely, if ever, enter the abscess cavity. Certain chronic abscesses, with a patent communicating bronchus, may fill well. The value of the procedure, except in isolated instances, is dubious.

*Aspiration*—Attempts at needling the abscess cavity in acute putrid abscess are fraught with hazard, and mentioned only to be condemned. In such circumstances, aspiration can serve no useful purpose, and the danger of causing a putrid empyema is so great that the procedure should never be undertaken.

*Treatment*.—To Neuhof should go the credit of crystallizing the modern concept of lung abscess as being primarily a surgical disease, and of demonstrating that it may be safely treated in one stage with a mortality of about 2 per cent. With the diagnosis established, then, and definitive surgical treatment the aim, the policy followed in my clinics is to bring the patient to a successful operation at the earliest moment when it is demonstrated that the case under consideration is one that will not heal spontaneously. Procrastination is useless and hazardous in the great majority of cases.

With this in mind, all other forms of therapy should be considered tentative adjuncts until such a decision is arrived at.

*Rest in Bed*—Obviously all patients with acute lung abscess should be confined strictly to bed.

*Postural Drainage*—Patients who are raising sputum in any amount should take postural drainage unless the general condition is so poor as to contraindicate it. In order to be effectual, postural drainage is preferably undertaken in such a way as to be as continuous as possible. Thus, if the disease is in the lower lobes, the patient should lie continuously in the prone position with 12-inch blocks under the foot of the bed. Various devices have been evolved to facilitate continuous and intermittent postural drainage. Singer has invented a bed which may be adjusted to any position. For practical purposes, intermittent postural drainage is carried out at two-hour intervals during the day, and the patient is awakened once during the night. The patient must be carefully instructed in order that effectual dependent drainage is obtained. Putting the head over the side of the bed and coughing does not suffice. Frequently, the patient will discover a position which produces the best drainage in his particular case.

*Continuous Oxygen*—Since anaerobes play an important part in the symbiotic infection in lung abscess, it has been recommended that high concentrations of oxygen be administered continuously by means of a suitable well-fitted mask. Evaluation of this form of therapy is necessarily difficult, but the rationale seems reasonable. We have used it in only one case in which there was temporary improvement but eventual drainage. It deserves further trial.

*Drugs*—In the past, a wide variety of drugs has been employed in the treatment of lung abscess. The arsenicals, as used in the treatment of syphilis, have been extensively used while the sputum contained

spirochetes. However, it may be said that there has been no great preponderance of evidence in favor of one or another of these drugs. Recently the advent of penicillin has altered this aspect of the problem at least to some extent. We have observed 2 abscesses clear rapidly with vigorous penicillin therapy. We have observed two others regress and then become stationary and require drainage. In all cases, however, the sputum rapidly changed in character so that it was no longer foul. The drug should be administered intramuscularly in doses of 15,000 units every three hours, a total of 120,000 units each twenty-four hours, as long as improvement continues. It has also been recommended that penicillin be administered by the inhalation method using a special nebulizer actuated by oxygen. By this method, 20,000 to 50,000 units are inhaled in a fine mist every two or three hours, and it is stated that effectual blood levels are attained concomitantly by absorption from the pulmonary circulation. If this method is used, however, Anderson believes it should be supplemented by intramuscular penicillin as outlined above.

It is too soon to evaluate this form of therapy, but it should be used in all cases of lung abscess as soon as the diagnosis is made. Certainly there has been improvement in the general condition in every case we have observed. The pitfall will be to prolong its use after it is no longer effectual.

*Operative Treatment*—Many operative procedures have been employed with the development of thoracic surgery only to be discarded as their usefulness has been disproved. These include phrenic interruption, various packs and plombages, thoracoplasty and pneumothorax, the last being an extremely hazardous procedure with a uniformly high incidence of putrid empyema. Operative procedures in use today are discussed below.

1 *Bronchoscopy*—The diagnostic value of this maneuver has already been mentioned. The most bronchoscopy can offer as a therapeutic measure is temporarily to improve drainage by the removal of granulations and shrinkage of the mucosa. It can aid in the removal of inspissated secretions which the patient is unable to raise himself. It should not, however, be expected to effect a cure, nor should it be persisted in as a definitive form of therapy.

2 *Cavity drainage (pneumonotomy)*—As has been stated above, the old concept of waiting six weeks to three months for complete "localization" of a lung abscess before undertaking drainage has passed into limbo due largely to the writings of Neuhof. It may be stated didactically here that drainage, preferably in one stage, should be undertaken as soon as it is evident that the lesion is not improving clinically and by roentgenograms. Such a decision is usually taken in less than two weeks from the time treatment, as outlined above, has begun. A discussion of technic is not germane to this article. Suffice it to say that the operation is performed under local and regional anaesthesia and

in the hands of an experienced thoracic surgeon is not technical difficult Following early drainage, improvement is prompt and dramatic in the vast majority of cases Packing of the abscess cavity upon healing occurs is necessary, usually a matter of a few weeks

3 *Lobectomy and pneumonectomy*—In long-standing chronic abscess with extensive pulmonary destruction and associated secondary bronchiectasis total extirpation of the diseased lobe, lobes or lung offers the only hope of cure. While the mortality is somewhat high in this disease than for resections of the lobes or lung in bronchiectasis for example, it is steadily being lowered and with the use of penicillin promises to be a thoroughly feasible undertaking with a mortality perhaps under 10 per cent.

*Complications.—Empyema*—Perforation of the abscess which is most invariably peripherally located, extension of infection to the pleura, or ill-advised attempts at aspiration result in putrid empyema a common complication Promptly recognized and immediately treated by extensive rib resection and open drainage, a high recovery rate (90 per cent) may be expected Temporizing measures such as aspiration or closed drainage result in a much higher mortality (50 per cent)

*Hemorrhage*—Bleeding of varying degrees frequently occurs as complication of lung abscess due to the erosion or tearing of a vessel It is frequently fatal As a desperate measure, emergency lobectomy may be attempted If the abscess has already been drained, ligation and cauterization of the vessel or packing of the cavity usually will control the bleeding

*Spread of the Infection*—Intrapulmonary bronchogenic spread to the same or to the uninvolved lobes due to spilling of infected secretions is a complication resulting frequently in a fatal fulminating pneumonia or gangrene Penicillin has proved of value in this complication The complication will occur less frequently with early drainage

*Cerebral Abscess*—Metastatic spread of the infection to the brain by way of the vertebral veins is a not uncommon complication In our experience it has been invariably fatal Recently it has been recognized that ligation of the intercostal veins at the time of drainage of abscess is a necessary addition to the technic By this maneuver, the prevention of the spread of septic thrombi into the vertebral veins is accomplished

## BIBLIOGRAPHY

### *Primary Carcinoma of the Lung*

- Alexander, J Circumscribed Intrathoracic Neoplasms J.A.M.A., 119 395-396, 1942  
 Dorn, H F Incidence and Prevalence of Cancer of Lung Pub Health Rep 58 1265-1271, 1943  
 Graham, E. A Indications for Total Pneumonectomy Dis Chest, 10 87-94, 1945  
 Rienhoff, W F, Jr Present Status of Surgical Treatment of Primary Cancer of Lung J A M A 126 1123-1128, 1944

*Bronchiectasis*

- Perry, K. M. A. and King D. S., Bronchiectasis Study of Prognosis Based on Follow-up of 400 Patients. *Am. Rev. Tuberc.*, 41 531-548 1940
- Riggins, H. McL. Bronchiectasis Morbidity and Mortality of Medically Treated Patients. *Am. J. Surg.*, 54 50-67 1941

*Lung Abscess*

- Neuhof H. Acute Putrid Abscess of the Lung *Surg., Gynec. & Obst.*, 80 351-354, 1945
- Shaw R. R. Pulmonary Abscess Value of Early One-stage Operation. *J. Thoracic Surg.*, 11 453-463, 1942



## VITAMINS IN PRESENT DAY TREATMENT

HAROLD JEGHERS, MD, FACP\*

THERE appears to be a growing tendency to regard vitamin deficiency as synonymous with nutritional deficiency. This often leads to the erroneous concept that the treatment of any nutritional deficiency consists of the exhibition of one of the many multivitamin capsules or pills now so readily available. Such an approach overlooks the correction of the basic dietary habits responsible for the deficiency and further does not distinguish between the use of natural and complete vitamin substances in contradistinction to the use of a limited number of crystallized or concentrated pure vitamins. It is well to recall at this point that the vitamins now commonly used therapeutically constitute only part of the total vitamins known or still to be isolated and further that vitamins constitute only about a third of the forty or more nutrients required by the human body.

Nutrition is a relatively new and rapidly growing medical science. There is every reason to believe that the practical application of nutritional knowledge will play an ever-increasing role in the medical practice of the future. Its potentialities for preventive medicine appear enormous. There have been many pleas that the physician assume leadership in this field. The praiseworthy results of the application of nutritional principles in the practice of pediatrics are well known. There is much to be said for the continuation of these principles in the practice of adult medicine.

Proper nutrition has been accorded a place, along with heredity, in the control of longevity. The literature contains cautious suggestions that long-continued inadequacy of diet may be a factor in the early development of degenerative diseases. To be truly effective, proper dietary principles must be applied early and continued throughout life. It has been aptly stated that the practice of geriatrics commences where the practice of pediatrics leaves off. Any ill effects of a lifetime of incorrect diet cannot be righted, once old age is reached. The family doctor should make every effort to promulgate this thesis. It is earnestly suggested that an inquiry into a person's habits of eating and recommended dietary changes should be made a routine part of the annual health checkup now being widely recommended to the public.<sup>1</sup>

The widening concept of deficiency disease to include deficiency of

---

From the Fifth and Sixth (Boston University) Medical Services, Boston City Hospital and the Department of Medicine, Boston University School of Medicine, Boston.

\* Associate Professor of Medicine, Boston University School of Medicine, Physician-in-Chief, Fifth Medical Service, Boston City Hospital, Assistant Physician, Clinical Staff, Evans Memorial, Massachusetts Memorial Hospitals.

other nutrients than the vitamins and the application of this knowledge prophylactically as well as therapeutically constitutes at present the really intelligent approach to nutritional problems in present-day medical practice. Although this clinic is limited to the use of vitamins I trust that the broader aspects mentioned above will be constantly kept in mind.

#### CAUSES OF VITAMIN DEFICIENCY

Ordinarily vitamin deficiencies are caused by an inadequate diet, which results most commonly when the major caloric intake is in the form of refined foods such as white flour, sugar, lard and polished rice. Within recent years many of these refined foods have been nutritionally improved or enriched by the addition of one or more vitamins or minerals. It is well to realize that enrichment of food is not yet universal, that the number of nutrients added is limited, and that the enriched foods now available still do not equal natural foods in all respects.

One not uncommonly hears expressed at present the belief that full use of the program of enrichment of foods will ultimately lead to the complete disappearance of nutritional deficiencies and the need for any knowledge of these disorders. It is unlikely that such a utopia will ever be realized. Furthermore, many factors other than the use of refined foods may produce deficiency disease, and these will always be present as long as disease exists. The long-continued use of an unbalanced diet of even natural foods may eventually lead to deficiency of one or more nutrients. Alcohol, by supplying caloric energy but no vitamins, has been and will continue to be one of the commonest causes of deficiency disease. Therapeutic diets (such as elimination diets for allergic disturbances, diets for reduction of weight, for peptic ulcer and gallbladder disease) if not properly supplemented often are at fault. Numerous diseases by producing anorexia, vomiting or diarrhea interfere with proper food intake or its absorption. The liver is essential in the storage, conversion or utilization of almost every vitamin and disease of this organ invariably leads to vitamin deficiency. Fever, increased metabolism and physical exertion increase the need for certain of the B complex factors. Pregnancy, lactation and rapid growth during childhood and puberty all strikingly increase the need for nutrients as contrasted with more fixed requirements of grown adults. The water-soluble vitamins are lost during excessive perspiration or polyuria. Obstructive jaundice, sprue, intestinal fistulas and pancreatic disease interfere with vitamin absorption. Certain therapeutic agents such as alkali or mineral oil influence gastrointestinal absorption. There is growing evidence that some vitamins are synthesized in the gut and that use of drugs which affect the gastrointestinal flora may adversely affect this mechanism.<sup>2</sup> Likewise vitamin deficiency may result because of some defect in the metabolism of the vitamin within the body. This appears to be particularly true with regard

to vitamin A.<sup>8</sup> Abnormality of vitamin metabolism is being shown with increasing frequency to be the responsible etiologic factor in a wide variety of hitherto unexplained disorders. This has been especially so with regard to certain skin disease. It is thus apparent that vitamin deficiency will be an ever-present problem in medical practice and apparently one destined to become more complex rather than more simple.

**Dental Causes of Vitamin Deficiency**—A much neglected phase of medicine is the causal relation of inadequate dentition to nutritional deficiency. This appears to be especially true in the elderly age group. Many older persons and occasionally those from younger age groups, have difficulty chewing solid food, especially meat, due to inadequate dentition. Pyorrhea, loose teeth, dental caries, extensive dental extractions, lack of artificial dentures or artificial dentures not used because of discomfort are common dental causes for vitamin deficiency. I have been strongly impressed with this factor in evaluating the cause of deficiency syndromes in patients studied on the medical wards and in the outpatient department of the Boston City Hospital. It is not uncommon to find patients who for months to years have eaten no meat or other solid foods requiring much chewing. Such persons should receive dental advice and an attempt made to correct this difficulty. If for any reason this is not possible, advice should be given with regard to soft or liquid foods that can be readily eaten but that will nevertheless be nutritionally adequate.

Ill-fitting dentures, aside from causing trouble in eating, may result in constant drooling of saliva. Over a period of time this results in angular fissures at the corners of the mouth, varying degrees of labial change and even glossitis. This syndrome is often mistaken for the changes produced by riboflavin deficiency, in fact Ellenberg and Pollock<sup>14</sup> called it "pseudo-ariboflavinosis." Treatment with vitamin B factors is of no avail and only suitable dental treatment will result in improvement. The "pseudo-ariboflavinosis" is by no means a rare condition.

#### DIAGNOSIS OF VITAMIN DEFICIENCY

Recognition of vitamin deficiency depends on (1) a history of an inadequate diet or presence of some disease or physiologic disturbance interfering with full utilization of ingested food, (2) the presence of specific clinical symptoms and physical signs, (3) laboratory tests and (4) characteristic response to indicated vitamin therapy.

**Laboratory Tests**—On the whole there are but few specific laboratory tests for the recognition of vitamin deficiency. Furthermore, these procedures are complicated and but rarely available even in well equipped hospitals. Youmans and Patton<sup>4</sup> have given a good discussion of them.

— Impaired dark adaptation of the eyes as determined by a photom-

eter test and the lowered blood level of vitamin A and carotene may be indicative of vitamin A deficiency

Decreased urinary excretion of thiamine, niacin and riboflavin, particularly after a test dose, may be used to detect deficiencies of these water-soluble factors of the vitamin B complex. Blood pyuric acid level is often used as an indirect measure of thiamine deficiency. Vascularization of the cornea, as detected by use of the slit-lamp and corneal microscope, occurs in riboflavin deficiency but is nonspecific and produced by other means.

Lowered or absence of vitamin C in blood plasma, and particularly a diminution or absence of vitamin C from the platelet-white cell fraction of the blood, is highly diagnostic of vitamin C deficiency.

Decreased blood prothrombin level or increased prothrombin time indicates hypoprothrombinemia, this is indirectly indicative of vitamin K deficiency. Bleeding is likely to occur when the blood prothrombin level reaches 35 to 15 per cent of normal. This test is available in almost every hospital laboratory and should always be performed in persons manifesting any disturbance likely to interfere with the absorption of the fat-soluble vitamin K. These situations include prolonged high fever, neonatal period, chronic diarrhea, sprue, obstructive jaundice, liver disease and pancreatic disease.

Elevated serum phosphatase, diminution of blood phosphorus and specific changes in roentgenogram of bones are laboratory proof of rickets (vitamin D deficiency) in children.

**Clinical Symptoms and Physical Signs.**—Diets are complex and if deficient in one vitamin are likely to be deficient in others. As a result, long-continued use of deficient diets produces complex and multiple deficiency syndromes. Even when one clearly defined clinical syndrome seems to predominate, it is very likely that other deficiencies are present in subclinical forms. In fact, treating a recognizable syndrome with one pure vitamin with no change in the responsible inadequate diet may eventually allow the subclinical deficiencies to progress to a recognizable degree. It is well to recall also that a short period of severe vitamin depletion may produce a clinical picture quite different from the prolonged, but mild, depletion of the same vitamin. Furthermore, the clinical syndrome produced in children by any specific vitamin deficiency may be different from that produced in an adult.

It is impossible in a paper of this type to describe in detail the symptoms and signs of all the clearly delineated vitamin deficiency. These have been described numerous times<sup>5, 6</sup> and no doubt all doctors have some journals, monographs or reference works to consult in this regard. The more clearly defined vitamin deficiency syndromes include night blindness, phrynodermia (hyperkeratosis follicularis), xerophthalmia, keratomalacia, Darier's disease, Wernicke's syndrome, peripheral neuritis, beri-beri heart disease, scurvy, vitamin P deficiency

pellagra, niacin deficiency encephalopathy, sprue, rickets, osteomalacia, arboflavinosis syndrome, certain types of cirrhosis, and hemorrhagic hypoprothrombinemia. It has been my personal impression, based on observation of clinical material at Boston City Hospital for the past twelve years, that the above syndromes were more frequent five to ten years ago but are still seen with a fair degree of consistency, and that they are by no means limited to persons addicted to alcoholism. Furthermore, although the grosser degrees of vitamin deficiency have become rarer, milder and subclinical, vitamin deficiencies are still very prevalent. Unfortunately the members of this latter group are considerably more difficult to diagnose, and only by attention to clinical minutiae, a careful dietary history and prompt improvement with disappearance of clinical signs and symptoms following vitamin therapy can they be recognized.

Field and his associates<sup>7</sup> have given an excellent account of the features of atypical and mild pellagra. Ruffin<sup>8</sup> has discussed the recognition of early deficiency states. I have been particularly impressed with the appearance of the tongue as a key to the recognition of mild vitamin deficiency.<sup>9</sup> The lingual papillae, especially the filiform papillae, appear to be sensitive to metabolic changes produced by vitamin deficiency, and tend to desquamate producing a tongue which is smooth and red in appearance. At times it is scarlet red and suggestive of niacin deficiency glossitis, or the papillae may be flattened and the tongue magenta in color, findings indicative of riboflavin deficiency. More commonly the tongue is simply smooth due to loss of papillae and beefy red in color, a condition designated as atrophic glossitis. Atrophic glossitis is frequently present in vitamin B complex deficiency, riboflavin deficiency, pellagra, pernicious anemia, Plummer-Vinson syndrome, sprue, pernicious anemia of pregnancy, chronic dysentery, intestinal stricture or fistula, infestation with broad fish tapeworm and achlorhydria. The presence of atrophic glossitis is an indication for therapy with liver extract or yeast. That the atrophic glossitis is often indicative of B complex deficiency is shown by the striking regeneration of papillae and restitution of the normal pinkish-white color of the tongue when proper therapy is instituted.

There are a wide variety of skin changes indicative of mild to severe vitamin deficiency. These have been discussed in detail elsewhere.<sup>8</sup> Likewise, changes in the external membranes of the eye may give a clue to the diagnosis. Mild thiamine deficiency may resemble neurasthenia or chronic nervous exhaustion.<sup>10</sup> With practice a surprising number of these clinical minutiae can be detected. After proper therapy is instituted disappearance of these minor clinical findings should be periodically searched for as this constitutes suggestive evidence of their deficiency origin.

**Dietary History**—A reliable dietary history is difficult to elicit, and is much neglected phase of history taking. The average physician feels much more competent to take a history and evaluate system com-

plaints (e.g., cardiorespiratory) With practice, however, one can become equally adept at evaluating diets and the patient's nutritional status. Some knowledge of food and nutrition of course is essential but this can be readily acquired. There are numerous well written monographs and shorter treatises available on this subject. A knowledge of diet is useful not only in searching for deficiency disease, but in many other phases of medical practice (e.g., diabetes mellitus, obesity, underweight, nephritis and peptic ulcer). The development of potent therapeutic agents to control infectious diseases or endocrine disorders has tended to accentuate the search for better management of all types of metabolic disorders. It is therefore likely that diet and nutrition will receive an increasing interest by the research worker.

The following outline, used on the Boston University Medical Services at Boston City Hospital as part of the general history, is suitable for securing a reasonably satisfactory dietary history.

## DIETARY HISTORY

Money spent per week for food		Regularity of meals	
No meals daily		Where eaten	
Highly seasoned foods		Idiosyncrasies of eating	
Use of following foods			
freely (F)	moderately (M)	rarely (R)	never (N) idiosyncrasy (I)
Meat	Milk	Potatoes	
Pork	Buttermilk	White Bread	
Liver	Cheese	Candy	
Eggs	Ice Cream	Sugar	
Fish	Puddings with Milk	Pastry	
Soy beans		Refined cereals	
		Rice	
		Macaroni	
		Spaghetti	
Whole Wheat Bread	Butter	Green veg	
Enriched Bread	Cream	Other veg	
Whole cereals	Peanut butter	Citrus fruits	
Beans	Other fats	Tomatoes	
	Margarine	Salads	
		Other fruits	
Evaluate intake of diet with regard to following			
Excess (E)		Adequate (A)	Low (L)
Calories	Carbohydrate	Fat	Protein
Vitamin A	B <sub>1</sub>	C	Niacin
			Riboflavin
			Minerals Ca
			Fe
Does patient take vitamin or mineral concentrates?			
Give a typical day's intake of food			
MORNING	NOON		EVENING
Summary of positive findings			

Its use in conjunction with a set of tables giving the caloric value, as well as the carbohydrate, fat, protein, vitamin and mineral content of common foods in terms of household measurements (ounces, cups, teaspoons, slices [of bread], one item of food [e.g., one egg, one pat of butter] etc.) will enable the doctor to make a dietary estimate reliable enough for routine clinical use. Tables of food values are widely available and can be readily secured for reference. In 1941, the Committee on Foods and Nutrition of the National Research Council published its recommended daily allowances for the various dietary nutrients (the so-called "yardstick for good nutrition")<sup>11</sup> These recommendations have been accepted and widely publicized by many authorities on nutrition. Probably every physician has a copy of these recommended daily allowances for specific nutrients in his file since it has been reprinted frequently.

The patient's dietary history can be evaluated by comparison with this recommended daily allowance. Proper attention should be paid to factors likely to increase body metabolism, interfere with gastrointestinal absorption, increase vitamin loss, or impair liver function. Under such circumstances vitamin deficiency may result even though a theoretically adequate diet was eaten. Inquiries should be made concerning the amount of alcohol consumed. Alcoholic patients are especially likely to consume an inadequate diet.

Patients often have trouble remembering the details of their diet. With ambulatory patients not critically ill it is very helpful to have them keep a careful food diary (type of food, amount and how prepared) of all food eaten for a week and postpone the evaluation of their diet until the next meeting. They should be expressly cautioned against any change in their eating habits while under this survey. With patients admitted to a hospital, or with those critically ill and in need of immediate therapy such a plan is not feasible and one must depend entirely on the patient's story.

Inquiry should be made as to the amount of money spent per person per week for food and whether meals are eaten at home or in a restaurant. Smith<sup>12</sup> has given some excellent advice for those who eat away from home. The paper by Guy<sup>13</sup> contains much practical advice with regard to diets. Idiosyncrasies of eating often are the cause of vitamin deficiency. There are many erroneous ideas concerning nutrition widely prevalent which need correcting. A typical example encountered recently was the housewife who separated the heavy cream layer from milk each day and discarded the skim milk portion because of the belief that all the nutrients in milk were contained in the cream layer. She was entirely unaware that the skim milk contained protein and minerals.

The dietary history form is arranged so that the first column lists foods rich in protein, the second foods rich in calcium, the third items high in carbohydrate, but poor in vitamins and minerals, the fourth

whole grains rich in vitamin B complex, the fifth foods rich in fats and lastly the vegetables and fruits. Persons who consistently avoid foods in any column except the third are more likely to develop a vitamin deficiency than those who select foods from each general group.

One must never fail to inquire whether the patient takes vitamin or mineral tablets, or capsules or concentrates as supplements to their diet. The patient must be impressed with the fact that the daily use of a vitamin capsule does not compensate for an inadequate diet. Correction of dietary habits is a more logical approach to this problem than attempts at elaborate supplementation to a basically poor diet. It is in this manner that physicians can counteract the prevalent belief that daily ingestion of a polyvitamin capsule makes any diet an adequate one.

#### TREATMENT OF VITAMIN DEFICIENCY

The principles of treatment of vitamin deficiency are relatively simple, and satisfactory therapeutic results usually follow rational use of the available methods or agents. Satisfactory treatment will, however, be conditioned by the accuracy of the clinical diagnosis and dietary history, and the ability to control underlying disease or physiologic conditions likely to interfere with absorption or metabolism of the diet and vitamins used.

**Diet**—The very essence of the control of any vitamin deficiency is the correction, if at all possible, of the dietary defect responsible for producing the deficiency. While this may not be essential for control of acute symptoms and signs it is essential if relapse is to be prevented in the future. Occasionally some disease exists which requires a special but unbalanced diet. Under such circumstances the unbalanced diet must be supplemented with natural vitamin concentrates of the proper kind and of potency sufficient to compensate for the dietary defect.

**Vitamin A**—The recommended daily allowance of vitamin A for the adult is 5000 U.S.P. or international units. The majority of the capsules now available contain this dose. For special therapeutic purposes capsules containing 25,000 or 50,000 units are available. Vitamin A is indicated in the treatment of night blindness, xerosis and phrynoderma. It is likely that either prolonged low grade vitamin A deficiency or some disturbance in the internal metabolism of this vitamin (dysvitaminosis A) may be the responsible etiologic mechanism for a variety of skin disorders. The literature contains claims<sup>3</sup> that Darier's disease, pityriasis rubra pilaris, ichthyosis Sjörgen's syndrome, dry skin, dryness and brittleness of hair, brittleness of nails, lichen spinulosus, vernix caseosa, keratosis blenorrhagica, callosities and acne may be in whole or in part produced by this mechanism. Its importance in Darier's disease appears to be best substantiated in this regard. For others of these, confirmatory studies are still awaited. Use of vitamin A for the treatment of hypertension and color blindness is not generally accepted.



Night blindness and xerophthalmia respond readily to moderate doses of vitamin A (10,000 to 20,000 units) continued for several weeks to two months or more. Skin lesions attributed to vitamin A deficiency or dysvitaminosis A for the most part respond slowly to therapy and require large doses orally (50,000 to 200,000 or more U.S.P. units per day) for months and perhaps years. When large doses are required, capsules of 25,000 or 50,000 units should be prescribed. Persons with dysvitaminosis A may require large doses of vitamin A to maintain improvement. Parenteral vitamin A therapy is but rarely indicated (e.g., in sprue, chronic diarrhea, obstructive jaundice, dysvitaminosis, celiac disease and pancreatic disease). Both bile and pancreatic lipase are necessary for its proper absorption.

**B Complex Vitamins**—The B vitamins include thiamine, riboflavin, niacin or niacinamide, pyridoxine, pantothenic acid, choline, inositol, para-aminobenzoic acid, folic acid, biotin and perhaps others. Although almost all of these are available commercially in synthetic form, only thiamine, riboflavin and niacin have well established uses in clinical practice. There is a growing but still controversial literature concerning the others.

Thiamine, riboflavin and niacin are prescribed by weight. The recommended dosage for therapeutic purposes should be at least several times the optimal daily requirement as recommended by the Committee on Foods and Nutrition of the National Research Council.<sup>11</sup> For example, a 70 kg man, moderately active, needs 18 mg of thiamine, 27 mg of riboflavin and 18 mg of niacin daily. For gross deficiency of these vitamins, 10 to 30 mg of thiamine, 5 to 20 mg of riboflavin and 100 to 300 mg of niacin could be prescribed. Ordinarily these vitamins are given orally in daily divided doses. Where indicated they may be given parenterally. Parenteral preparations are commercially available which contain adequate amounts of thiamine, riboflavin, niacin, pyridoxine and calcium pantothenate. Niacinamide is commonly used in place of niacin (nicotinic acid) unless the vasodilator effect of the latter substance is specifically desired. The therapeutic dose of the B vitamin should be continued for one to several weeks or until the clinical deficiency is corrected, after which the amount required daily can be reduced to the optimal daily requirements.

While the synthetic B vitamins are indicated in the treatment of gross deficiency syndromes it is well to supplement the therapeutic regimen with one of the natural sources of the complete B complex. If the ordinary daily diet is to be supplemented, vitamin B complex in natural form is preferable to a capsule containing a limited number of the synthetic B vitamins.

**Natural Sources of B Complex**—There are a number of natural substances containing all the members of the vitamin B complex. These include liver extract, wheat germ, brewers' yeast, autolyzed yeast and

rice polishings. Wheat germ can be mixed with cereal. The vitamin content is listed on the package usually in terms of thiamine and riboflavin and from this one can judge the daily amount required.

Oral liver extract preparations are relatively expensive and are not commonly used as a source of B vitamins. Parenteral liver extract, however, is widely used for this purpose. It is commonly stated that crude liver extract (fewest U.S.P. units of antipernicious anemia factor per cubic centimeter) is a better source of the B vitamin than concentrated liver extract. The recent study by Clark<sup>16</sup> would seem to indicate that both are comparable in their vitamin content. He found the averaged values of several concentrated liver extracts containing 15 units of antipernicious anemia factor per cubic centimeter was 0.55 mg. of riboflavin, 4.8 mg. of niacin and 1.97 mg. of pantothenic acid per 5 cc., while comparable preparations of crude liver extracts containing 2 units of antipernicious anemia factor per cubic centimeter contained 0.28 mg. of riboflavin, 4.13 mg. of niacin and 1.81 mg. of pantothenic acid per 5 cc. It is well to recall that the thiamine content of parenteral liver is negligible. Therefore, thiamine should be given in addition if liver extract is the main source of vitamin B complex therapy.

Autolyzed brewers' yeast is a good source of vitamin B complex. In our experience at Boston City Hospital it has been most acceptable to patients when given dissolved in boiling hot water. In this form it resembles beef bouillon. Dosage can be judged from the analysis on the container using the thiamine and riboflavin content as a guide.

Brewers' yeast, powdered or in tablet form, is probably the most satisfactory source of vitamin B complex for oral use. Potency varies with different brands. Many patients have trouble taking the number of yeast tablets recommended and prefer the yeast powder instead. Spies<sup>8</sup> has recommended its use in a mixture of 20 per cent dried brewers' yeast by weight and 80 per cent peanut butter. This is a palatable mixture. It is also commonly mixed in milk, chocolate milk shakes or malted milk shakes. The two following milk mixtures have been extensively used at Boston City Hospital in treatment of patients with nutritional deficiencies. They are particularly desirable for patients unable to chew solid food, for use during acute illnesses or to supplement other diets. The formula for the skim milk mixture as given makes a volume somewhat more than a quart, the use of 16 instead of 24 ounces of skim milk makes 1 quart. Mixing increases the final volume. The sodium chloride content is less than 2 gm. per quart. The mixture is flavored with chocolate syrup which is not included in the above calculations and adds slightly to the carbohydrate and fat. If desired, 1 to 4 teaspoonfuls of malted milk can be used with or in place of chocolate syrup as a flavoring agent. The orange juice in the mixture is readily accepted. If it is left out, ascorbic acid tablets should be prescribed as a supplement.

Fifteen grams of brewers' yeast powder is added to each quart of mixture. This amount gives no detectable taste, adds approximately 7.2 gm of protein and 5.8 gm of carbohydrate, and is generally accepted by patients.

FORMULA FOR SKIM MILK MIXTURE

	Carbohydrate	Protein	Fat
	Gm	Gm	Gm
6 oz orange juice	16.95		
4 oz Karo syrup	88.8		
6 egg whites		25.8	6
100 gm skim milk powder	38.8	35.4	1.7
24 oz skim milk	33.9	25.8	5.1
Total	178.45	87.0	7.4
Calories	1128		

The vitamin content of the skim milk mixture as given in the formula with added yeast powder is approximately 2.5 mg of thiamine, 1.8 mg of riboflavin, 6.5 mg of niacin, 1.5 mg of pantothenate, 0.6 mg of pyridoxine, 45 mg of ascorbic acid as well as other B complex factors. The vitamins except niacin and A and D, about equal the optimum daily allowances recommended by the National Research Council.

The protein is biologically highly active. The fat is low, but the amount of carbohydrate and the total calories are low in proportion to the amount of protein present. This mixture has been widely used for diets of patients with liver disease because of its high protein and carbohydrate and low fat content. It is very useful as a high protein-high vitamin supplement to the patient's routine diet.

FORMULA FOR WHOLE MILK MIXTURE

	Carbohydrate	Protein	Fat
	Gm	Gm	Gm
32 oz whole milk	45.2	34.4	32
100 gm skim milk powder	38.8	35.4	
3 whole eggs		18.0	18
Total	84.0	87.8	50
Calories	1137		

This mixture can likewise be supplemented with Karo syrup, orange juice, and brewers' yeast as described for the skim milk mixture and these add to the protein and carbohydrate value. Likewise it may be

flavored with chocolate or malted milk. Ascorbic acid tablets can be given to the patient if orange juice is not included.

Because of their low salt content these mixtures are suitable for the main source of nourishment and fluid for cardiac patients.

Other Vitamins—The use of ascorbic acid, vitamin D and vitamin K are well standardized and will not be discussed here.

## BIBLIOGRAPHY

1. Jeghers, H. Nutrition. *New England J. Med.*, 225:687 1941.
2. Editorial Review. Synthesis of Vitamins in the Bowel. *Lancet*, 2:854 1944.
3. Jeghers, H. Skin Changes of Nutritional Origin. *New England J. Med.*, 228:678, 714 1943.
4. Youmans, J. B. and Patton, L. W. The Laboratory Diagnosis of Nutrition Deficiencies. *Clinics*, 1:303 (Aug.) 1942.
5. Jolliffe, N. and Stern, M. Objective Manifestations of Nutritional Deficiency Diseases. *Clinics*, 1:282 (Aug.) 1942.
6. Spies, T. D. and Butt, H. R. Vitamins and Avitaminoses. Chapter 8 in Duncan, G. G., *Diseases of Metabolism*, Philadelphia, W. B. Saunders Co., 1942.
7. Field, H., Jr., Parnall, C., Jr. and Robinson, W. D. Pellagra in Average Population of Northern States. *New England J. Med.*, 223:307 1940.
8. Ruffin, J. M. Early Deficiency Diseases. Their Recognition and Treatment. *M. CLIN. NORTH AMERICA*, 27:485 1943.
9. Jeghers, H. Appearance of the Tongue as an Index of Nutrition Deficiency. *New England J. Med.*, 227:221 1942.
10. Wilder, R. M. Thiamine Deficiency. *M. CLIN. NORTH AMERICA*, 27:409 1943.
11. Committee on Foods and Nutrition, National Research Council. Recommended Dietary Allowances, 5 pp. Washington D. C., Nutrition Division Federal Security Agency 1941.
12. Smith, A. H. Teaching Nutrition to People Who Take Their Noon Day Meals Out. *Ohio State M. J.*, 38:117 1942.
13. Guy, R. A. Vitamins and the General Practitioner. *M. CLIN. NORTH AMERICA*, 26:1347 (Sept.) 1942.
14. Ellenberg, M. and Pollock, H. Pseudo Ariboflavinosis. *J.A.M.A.*, 119:72 1942.
15. Clark, G. W. Vitamin Content of Liver Extracts for Parenteral Use. A Comparison of Crude and Concentrated Preparations. *Am. J. M. Sc.* 1945.

# THE PRESENT STATUS OF SULFONAMIDE THERAPY

FRANCIS C LOWELL, M D \*

APPROXIMATELY six years have passed since the sulfonamide drugs became available for use on a scale sufficiently large to make clinical evaluation possible in a wide variety of diseases. During this period, new forms of sulfonamides have made their appearance from time to time, all of them, however, resembling each other in their mode of action and most of them differing principally in their solubility, their rate of absorption from the gastrointestinal tract and their rate of excretion by the kidney. All the commonly used sulfonamides are inhibited in their antibacterial action by para-aminobenzoic acid and to a variable extent by pus and necrotic tissue. These drugs also have in common the tendency to cause toxic reactions and careful supervision of the patient receiving a sulfonamide is necessary.

The biggest single change in the use of the sulfonamide drugs has been brought about by the advent of penicillin, which has recently become available for general use in this country. This can only be given by repeated injection at the present time, a fact which restricts its use and makes a sulfonamide the drug of choice under certain circumstances, even when penicillin may be more effective, and even though penicillin has the further advantage of producing very few toxic reactions.

With sulfonamides and penicillin available, the indications for serum treatment of infections due to such organisms as the pneumococcus and meningococcus are indeed rare. It is to be remembered, however, that gram-negative organisms, such as the influenza bacillus and Friedlander's bacillus, are entirely unaffected by penicillin and certain infections caused by them may best be treated with a sulfonamide and a specific antiserum.

The sulfonamides have been used for the prevention of recurrences of rheumatic fever and in the armed forces as a means of stopping or preventing epidemics of meningococcal and streptococcal infections. With proper control of the conditions under which the drugs are given, good results have been obtained with few and usually only mild toxic reactions. However, it seems unlikely that these measures can be effectively applied to civilians under the usual conditions of medical practice.

---

From the Evans Memorial, Massachusetts Memorial Hospitals and the Department of Medicine, Boston University School of Medicine.

\* Assistant Professor of Medicine, Boston University School of Medicine, Associate, Evans Memorial and Assistant Visiting Physician, Massachusetts Memorial Hospitals.

## ADMINISTRATION OF THE SULFONAMIDE DRUGS

In the treatment of an infection in which a sulfonamide is indicated it is probably wise to give the drug in *full therapeutic dosage*, as indicated, in the accompanying table. If the infection is so mild that smaller doses seem adequate, chemotherapy is usually unnecessary.

## DOSAGE SCHEDULE FOR THE ADMINISTRATION OF THE SULFONAMIDE DRUGS TO ADULTS

Drug	Initial Dose		Maintenance Dose		Therapeutic Blood Levels, mg./100 cc.
	By Mouth	By Injection as a 0.5 to 5% Solution†	By Mouth	By Injection as a 0.5 to 5% Solution	
Sulfadiazine	4 gm.	5 gm.	1 gm. every 4 to 6 hours	2 gm. every 8 to 12 hours	8-15
Sulfamerazine			1 gm. every 6 to 8 hours	2 gm. every 12 hours	8-15
Sulfathiazole			1 gm. every 4 hours	2 gm. every 8 hours	4-8
Sulfapyridine			1 gm. every 4 hours	2 gm. every 8 hours	5-10
Sulfanilamide‡			1-1.5 gm. every 4 hours	3 gm. every 8 hours	8-15

The sodium salts of sulfadiazine, sulfamerazine, sulfathiazole and sulfapyridine should be used for parenteral administration. For subcutaneous injection the concentration of these should not exceed 1 per cent.

† Sulfanilamide is used as a 0.5-1 per cent solution for parenteral administration.

Exceptions to this are the treatment of mild urinary tract infections and the use of small doses of sulfonamide for prophylaxis in certain infectious diseases.

The *blood levels* of the various sulfonamide drugs which may be considered both safe and therapeutically effective are also shown in the table. Repeated determinations of the concentration of drug in the blood are necessary in order to insure satisfactory levels, and changes in dosage should be made if the level is too low or too high. In the presence of poor renal function the excretion of the sulfonamides may be delayed and the concentration in the blood may then reach high levels. When the concentration of a sulfonamide drug is determined, only the *free* or *unacetylated* form of the drug is measured in most laboratories. It is rarely necessary to determine the *acetylated* or *combined* form of the sulfonamide in the blood, except in patients with renal insufficiency who are given a sulfonamide for a prolonged period. Sulfanilamide and sulfapyridine are acetylated to a greater extent than the other sulfonamides.

Of the measures available for the prevention of toxic reactions to the sulfonamide drugs, the *administration of adequate quantities of fluid* is the most important. Sufficient fluid should be given to insure a urinary output in adults of 1500 cc. in twenty-four hours. In some patients, 2500 cc. of fluid daily will be sufficient, but patients with acute infections and fever may require 3000 cc. to 4000 cc. daily.

Fluids may be given orally in the form of soups, milk, fruit juices, normal saline and water or parenterally as saline, glucose and water in combination, so as to provide 10 to 15 gm of salt and a sufficient volume of fluid. In the presence of dehydration, the initial dose of sulfonamide should be accompanied by, or even preceded by, a sufficient quantity of fluid to insure hydration of the patient.

**Renal Complications**—Crystalluria, hematuria, renal colic, oliguria and anuria are complications of sulfonamide therapy, listed here in order of increasing seriousness. As renal complications are more frequent than any others during sulfonamide therapy, they should be watched for carefully. *Crystalluria*, that is, the finding of sulfonamide crystals in the spun sediment of freshly voided urine specimens, indicates that the conditions are present which predispose to renal complications and steps should be taken to increase the urinary output and to render the urine alkaline. The same may be said of *microscopic hematuria*. In neither instance is cessation of sulfonamide therapy necessary. *Gross hematuria, renal colic, oliguria and anuria* require immediate cessation of sulfonamide therapy followed as well by those measures just mentioned. In the presence of anuria, ureteral lavage with a warm alkaline solution may be indicated.

There is considerable evidence that the administration of alkali with a sulfonamide will reduce the tendency to those renal complications resulting from precipitation of the sulfonamide in the kidney. The base acts by raising the pH of the urine to 7 or higher, thereby increasing the solubility of the sulfonamide, especially the acetylated form, in the urine. Sodium bicarbonate may be given by mouth or sodium lactate (100 cc of one-sixth molar sodium lactate solution is equivalent to 14 gm of sodium bicarbonate) may be added to the solution of sulfonamide for parenteral administration. The amount of sodium bicarbonate necessary to raise the pH of the urine differs widely among patients and it is convenient and helpful to follow the urinary pH with nitrazine paper. In adults, an initial dose of 6 gm and a daily dose of 15 gm in twenty-four hours is usually sufficient. Patients who are nauseated and who are receiving a sulfonamide by mouth, may object to taking sodium bicarbonate in addition. Under such circumstances it may be wiser for the doctor to omit bicarbonate and to center his attention on insuring an adequate urinary output.

Severe renal damage during sulfonamide therapy may arise on some basis other than mechanical damage and obstruction due to precipitation of crystals. The pathogenesis of this complication is not clear. There develops tubular degeneration with increasing renal failure which may be fatal. The factors predisposing to this are not known but large dosage and high blood levels are not a sine qua non. The condition is characterized clinically by a decreasing urinary output, albuminuria, microscopic hematuria and white cells in the sediment.

Crystalluria may be absent. Treatment consists in the immediate cessation of sulfonamide therapy and the administration of fluids. Alkali may also be given but its effectiveness in this condition is unknown.

**Other Toxic Reactions**—*Rash and fever*, which may occur together or separately, are probably due to the development of an allergy to the sulfonamide. They are usually not serious reactions, but it is advisable to stop sulfonamide therapy when they occur. In certain individuals having eczematous skin eruptions which have been treated with prolonged local application of a sulfonamide, a very severe systemic reaction with rash and fever may develop rapidly after a sulfonamide is given by mouth or parenterally. Such reactions may be so severe as to endanger the patient's life. No simple reliable test for sulfonamide sensitivity has been devised. Skin tests have been described but their practical application at this time is still in doubt. The administration of a small dose of a sulfonamide (0.5 gm) by mouth may cause, within a few hours, a rash, a rise in temperature, or both, in sensitive individuals, but tests of this kind may be hazardous.

*Acute hemolytic anemia* is a rare but dramatic complication occurring within one or two days of starting therapy. This reaction is dangerous and should be treated by (1) immediate cessation of sulfonamide therapy, (2) the administration of fluids and sufficient alkali to maintain the urinary pH above 7, and (3) transfusions as indicated by the degree of fall in the hematocrit or red count. A *slowly progressive anemia* is not uncommon during sulfonamide therapy. No treatment is required except transfusion if the anemia is marked. Sulfonamide therapy may be continued in the majority of cases.

A *progressive leukopenia* may develop slowly after several days of treatment. Where continued sulfonamide therapy is indicated, treatment may be continued unless (1) the percentage of polymorphonuclear cells falls below 50 per cent or (2) the total white count falls below 4000 with developing neutropenia. Daily white counts and smears should be made. Rarely, *agranulocytosis* develops, usually only after a week or more of treatment. In the face of this dangerous complication, sulfonamide therapy should be stopped. Secondary infection may be combated with penicillin, 15,000 to 20,000 units intramuscularly every three hours. Transfusion and pentnucleotide may also be given. In agranulocytosis arising from causes other than sulfonamide therapy the accompanying secondary infection may be treated with a sulfonamide if necessary in addition to penicillin.

#### INDICATIONS FOR SULFONAMIDE THERAPY

Before discussing individual diseases it should be emphasized that every attempt must be made to obtain as early as possible all the data and specimens necessary to make possible a definite bacteriologic diagnosis. When cultures are reported twelve to twenty-four hours later,



treatment may then be modified in the light of the bacteriologic findings. Grouping or typing of organisms should be carried out when possible.

**Pneumonia**—In view of the difficulty in distinguishing the bacterial pneumonias from primary atypical pneumonia (presumably caused by a virus), it seems advisable to treat all cases of severe or moderately severe pneumonia with chemotherapy at the outset. If after 48 to 72 hours of treatment there is no response and the clinical picture and bacteriologic findings indicate the absence of bacterial infection, chemotherapy may be stopped. The more severely ill patients should be hospitalized. Whether penicillin, sulfonamide, or both should be used will depend on the causative agent. If the cause is in doubt, especially if the patient is very ill, both penicillin and sulfonamide may be given.

It is to be noted that two important causes of pneumonia, the influenza bacillus and Friedlander's bacillus, are entirely unaffected by penicillin. Treatment here consists in full dosage of sulfadiazine or sulfamerazine and possibly the use of specific antiserum. This last is available for Friedlander's bacillus, type A and B, and for influenza bacillus, type B. The identification of types may be facilitated when it is recalled that the capsule of the influenza bacillus, type B, usually swells in the presence of type XXIX pneumococcus typing rabbit serum and often in the presence of type VI typing serum, and that of Friedlander's bacillus, type B, swells in the presence of type II pneumococcus typing rabbit serum. This information may be useful as pneumococcus typing serum is available in most laboratories.

**Meningitis**—The sulfonamide drugs are extremely effective in *meningococcic meningitis* and there is little reason at present to believe that penicillin alone would give better results. As the organism is highly sensitive to both drugs, combined therapy should be given to severely ill patients, especially those having a rash.

The treatment of meningitis due to the pneumococcus and streptococcus, organisms which are also susceptible to both sulfonamide and penicillin, consists in full dosage of a sulfonamide, preferably sulfadiazine, the intramuscular or intravenous administration of 200,000 units of penicillin daily and the intrathecal injection of 20,000 units of penicillin at twelve-hour intervals. Bacterial meningitis, especially pneumococcic, has a strong tendency to relapse when treatment is stopped, and for this reason treatment should be continued for at least ten days after culture of the spinal fluid has become negative, the sugar has returned to normal, and the cell count has fallen to 100 or less with a predominance of lymphocytes. Early diagnosis and treatment are of the utmost importance.

*Pneumococcic meningitis* still carries a high mortality and early intensive treatment is imperative. In addition to penicillin and sulfonamide therapy as outlined above, specific serum is available for the various pneumococcic types. If it is decided to give serum, this may

be given intramuscularly or intravenously in doses of 100,000 to 300,000 units after suitable precautions are taken. Serum should not be injected intrathecally. *Staphylococcic meningitis* requires prolonged treatment with both intramuscular and intrathecal penicillin and a sulfonamide in full dosage. *Staphylococci* are relatively insensitive to the sulfonamides and they vary greatly in their susceptibility to penicillin. Tests for the resistance of the infecting organisms to this drug are often helpful. Meningitis due to the *influenza bacillus*, which is unaffected by penicillin, requires prolonged treatment with full doses of sulfadiazine, sulfamerazine or sulfapyridine. Therapeutic rabbit serum for type B infections is available.

**Genitourinary Infections**—The colon bacillus which is penicillin-resistant, is the common cause of urinary tract infections and for this reason a sulfonamide drug especially sulfathiazole or sulfadiazine, is indicated. Small doses 0.5 gm three times daily, will frequently control mild infections, but in more severely ill patients full doses of the drug should be given. Sulfamerazine should be less effective, on theoretical grounds, because it is excreted less rapidly by the kidney. Penicillin may be used when a susceptible organism, such as the staphylococcus, is causing the infection.

Numerous instances of infection with sulfonamide-resistant strains of gonococcus are encountered in medical practice and, at the present time, penicillin is the drug of choice in gonorrhea. Clinical cure is achieved in a very high proportion of uncomplicated cases when a total of 100,000 units of penicillin is given intramuscularly in five doses of 20,000 units at three hour intervals. However, more prolonged treatment is often necessary in the presence of prostatitis, vesiculitis, arthritis and other complications. Syphilis and gonorrhea may occur together. In this event the short treatment of gonorrhea with penicillin may lead to much difficulty in the diagnosis of syphilis later.

**Dysentery**—Sulfadiazine appears to be the drug of choice in the treatment of dysentery. The drug should be given in full dosage and continued for a period of four days after cultures of the stools are negative for the infecting organism. Special care should be taken to provide a large fluid intake in order to insure an adequate urinary output.

#### THERAPEUTIC FAILURES

The nature and severity of the infection at the time treatment is started greatly influences the response to treatment and the incidence of complications. Difficult problems are presented by patients who appear to have an infection of a type which ordinarily responds readily to therapy, but who fail to improve after several days of therapy. A number of causes for such failure should be considered.

*Inadequate blood levels* of a sulfonamide may be present in patients receiving full therapeutic doses by mouth but in whom absorption from the gastrointestinal tract is slow. Also, certain patients may ex-

crete the drug in the urine more rapidly than others. The only way to recognize this difficulty is to make repeated determinations of the blood level. The dosage of drug may be increased until satisfactory levels are obtained. Patients receiving a sulfonamide by mouth who fail to attain adequate blood levels may be given supplementary doses of two or more grams intravenously.

The development of *sensitivity* to a sulfonamide drug, usually occurring after five or more days of treatment, may cause the persistence of fever and thus simulate a therapeutic failure. If a rash also appears, the correct cause of the fever is readily suspected, but in the absence of any skin manifestations there are no definite criteria by which one can recognize the condition. If drug fever is present, a fall in temperature follows cessation of therapy. This fall is rapid in patients who have been receiving sulfathiazole, occurring in twelve to twenty-four hours, but the fall is more delayed in the case of sulfadiazine and sulfamerazine where the rate of excretion is slower.

Occasionally the infecting organism is a *sulfonamide-resistant* strain. Larger doses or a different sulfonamide may be tried but usually little is gained in this way. Penicillin should be given if the organism is susceptible to this drug.

Pathogenic organisms are often present in the throat or elsewhere even though they may be playing no part in the patient's infection. This is a common source of *error in diagnosis* and when the correct cause of the infection is found, more effective treatment can often be given.

Patients who have a *complication*, such as empyema, abscess, osteomyelitis or endocarditis, may continue to have fever and leukocytosis in spite of intensive therapy. Renal infections associated with *stone* or *congenital defects* may also respond poorly to therapy. Treatment of the local condition is usually required before complete recovery will take place.

#### SUMMARY

The sulfonamide drugs are best given in full therapeutic doses in the treatment of most acute infections. Repeated determinations of the blood level are necessary in order to insure safe and adequate treatment. Toxic reactions must be recognized early.

The present-day treatment of many infectious states can be extremely effective when the cause and severity of the infection are known and when appropriate treatment is started early.

#### BIBLIOGRAPHY

##### *Renal Complications*

- Gilligan, D. R., Garb, S., Wheeler, C. and Plummer, N. Adjuvant Alkali Therapy in the Prevention of Renal Complications from Sulfadiazine. J.A.M.A., 122: 1160, 1943.

- Gilligan, D. R., Dingwall J. A. and McDermott, W. The Parenteral Use of Sodium Lactate Solution in the Prevention of Renal Complications from Parenterally Administered Sodium Sulfadiazine. *Ann. Int. Med.*, 20:604, 1944
- Murphy F. D., Kuzma J. F., Polley T. Z. and Grill, J. Clinicopathological Studies of Renal Damage Due to Sulfonamide Compounds: a Report of Fourteen Cases. *Arch. Int. Med.*, 73:433, 1944
- Lederer M. and Rosenblatt P. Death during Sulfathiazole Therapy: Pathologic and Clinical Observations on Four Cases with Autopsies. *J.A.M.A.*, 119:8, 1942

*Rash and Fever*

- Livingood, C. S. and Pillsbury D. M. Sulfathiazole in Eczematous Pyoderma: Sensitization Reaction to Successive Local and Oral Therapy. Report of Twelve Cases. *J.A.M.A.*, 121:406, 1943
- Cohen, M. H., Thomas, H. B. and Kalisch A. C. Hypersensitivity Produced by the Topical Application of Sulfathiazole. *J.A.M.A.*, 121:408, 1943
- Shaffer B., Lentz, W. J. and McGuire, J. A. Sulfathiazole Eruptions: Sensitivity Induced by Local Therapy and Elicited by Oral Medication. Report of Four Cases with Some Allergic Studies. *J.A.M.A.* 121:17, 1943

---

ERRATUM

In "The Use of Electrocardiograms in Medicine" by Harold M. Stewart, M.D., appearing in the May number the first paragraph on page 600 should read "In Figure 106 are shown the records of a patient who had electrocardiographic evidence of posterior base lesion and one year later evidence of anterior base lesion. He died shortly after this last accident. At autopsy, the scar of the first myocardial infarction was seen involving the basal region and the fresh infarction involving the apex of the heart."

## LABORATORY FINDINGS IN THE BLOOD AND URINE IN HEALTH AND DISEASE

STANLEY E BRADLEY, M D \*

As medical knowledge expands, the position of the laboratory in every field of medical practice becomes increasingly important. Its services are indispensable in modern diagnosis and treatment, particularly since chemotherapeutic methods of halting disease processes and of repairing the ravages of disease have proved their worth and come into universal use

The large number of procedures carried out in the routine laboratories of even small hospitals each year is indicative of this importance, but it is also indicative of misuse. It is apparent everywhere that many physicians use laboratory facilities unthinkingly. Laboratory studies are often demanded routinely on a hit-or-miss basis in the hope of easy diagnosis, frequently with the aim of impressing and pleasing the patient. This is unfortunate because it results in unnecessary labor in the face of manpower shortages, in a deterioration of standards and in unreasonable expense. In the last analysis, diagnosis devolves upon the physician, depending upon his observational skill and his perception of significant facts in data culled from the history, the physical examination, and, finally, the laboratory study. This task can never be safely shifted to the shoulders of laboratory personnel. On the other hand, there is abundant evidence that available facilities are not used efficiently. Not infrequently, intuition plays too large a role in guiding treatment. This is to be deplored because the accurate adjustment of chemotherapy requires an accurate knowledge of the system under treatment.

One important cause of these abuses lies in the staggering number of procedures now available and in the difficulty of keeping in mind the normal figures and causes of deviations. The tables that follow have been compiled with the purpose of providing for ready reference the range of normal values of a large number of blood and urine constituents. A list of some of the more important disorders in which changes are observed has been added. The tables are based on the physiological systems of the body that are disturbed by disease. It can be seen that a view of these data as primarily expressive of physiological states rather than of etiological factors is implicit in this arrangement. It is true that certain tests may be of great value in clari-

---

From the Evans Memorial, Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston

\* Instructor in Medicine, Boston University School of Medicine, Assistant Physician, Evans Memorial, Massachusetts Memorial Hospitals.

fying and defining causation but, by and large, the data tabulated here express what is *happening* in the body, not what is *causing* the disturbance.

On the whole, a policy of generalization has been followed. Thus such general expressions as diarrhea, vomiting and renal insufficiency and the like are used where possible. All renal diseases leading to renal insufficiency or nephrotic syndrome are to be considered as implicated under those headings. It should be understood, moreover, that these findings are not always found in the disorders listed, many, such as diabetes mellitus, show no derangement of electrolyte balance until severe changes such as ketosis and coma have set in. Abbreviations are defined in the text of the tables or are conventional. In addition, the following symbols are used (+) increased in, (—) decreased in, (N) normal or unchanged in, (B) concentration in whole blood, and (P) concentration in plasma.

Concentrations are given in terms of serum or plasma volume. No effort has been made to separate the two because the differences are insignificant for practical purposes. Proteins of course, are stated in terms of plasma concentration.

More exhaustive consideration of pathological alterations and details of the various procedures should be sought in the sources that have been freely drawn upon in the construction of the tables.

# 1 BLOOD VALUES OF IMPORTANCE IN EVALUATING STATES OF DEHYDRATION ACID-BASE BALANCE, ETC.

IN HEALTH		
	Millicquivalents per Liter	Milligrams per 100 cc.
Sodium	139-152	315-330
Calcium	4.5-5.5	9-11
Diffusible ion.	2.5-3.0	4.5-6.0
Potassium	4.1-5.6	16-22
Magnesium	1.6-2.5	1.8-3.6
Total Base (B)	145-160	
Bicarbonate (Carbon Dioxide Combining Power)		
adults	25-35	55-75 vol. per cent
children	20-30	45-65 vol. per cent
Chloride	90-110	330-390
		570-620
		as NaCl
Phosphorus—inorganic		
adults	0.5-1.0	2-5
children	0.75-1.25	4-7
Phosphorus—total		
adults		8-18
children		5-14
Sulfur (inorganic)	0.13-0.17	0.5-1.1
(ethereal sulfate)		0.1-1.0
Total organic acids	up to 10	

pH	arterial	7 30-7 49
	venous	7 33-7 52
Specific Gravity		1 0254-1 0288
Proteins—	total	6 5-7 5 gm per 100 cc
	albumin	3 8-4 4 gm per 100 cc.
	globulin	2 2-3 4 gm per 100 cc
	A/G ratio	1 4-2 2
	fibrinogen	0 2-0 6 gm per 100 cc
Blood Volume—	adults	2990-6980 cc (4635 cc)
	females	46 3-85 4 cc./kg body weight
	males	66 2-99 7 cc./kg body weight

## IN DISEASE

Na	(+)	Vomiting, renal insufficiency, nephrotic syndrome, occasionally cardiac decompensation, Cushing's syndrome, adrenocortical tumor
Na	(-)	Renal insufficiency, vomiting, diarrhea, excess sweating, starvation, diabetes mellitus, pregnancy, nephrotic syndrome, Addison's disease
Ca	(+)	Pyloric obstruction, hyperparathyroidism, acidosis, polycythemia.
Ca	(-)	Renal insufficiency, post-parathyroidectomy, infantile tetany, oxalic acid poisoning, osteomalacia, rickets, starvation, diarrhea, late pregnancy, nephrotic syndrome, steatorrhea, hyperthyroidism
K	(+)	Addison's disease, renal insufficiency, shock
K	(-)	Periodic familial paralysis, fever, nephrotic syndrome, Cushing's syndrome, adrenocortical tumor
Mg	(+)	Renal insufficiency
Mg	(-)	Occasionally in epileptic convulsion
HCO <sub>3</sub>	(+)	Alkali ingestion, vomiting, pulmonary emphysema, morphine poisoning, pneumonia, occasionally renal insufficiency
HCO <sub>3</sub>	(-)	Renal insufficiency, diarrhea, vomiting, excess sweating, starvation, dehydration, acid ingestion, oil of wintergreen and methyl alcohol poisoning, decompensation, Addison's disease, anesthesia
Cl	(+)	Diuresis due to chloride and sulfate diuretics, anesthesia, prolonged hyperventilation (hysteric and postencephalitic)
Cl	(-)	Addison's disease, starvation, vomiting, water and mercurial diuresis, alkalinizing salts, diabetes mellitus, pneumonia, occasionally diarrhea, nephrosis and acute nephritis
HPO <sub>4</sub>	(+)	Renal insufficiency, post-parathyroidectomy, occasionally osteomalacia, rickets and acute yellow atrophy of liver
HPO <sub>4</sub>	(-)	Hyperparathyroidism, rickets, osteomalacia, steatorrhea
SO <sub>4</sub>	(+)	Renal insufficiency, intestinal obstruction
Organic Acids	(+)	Starvation, diabetes mellitus, renal insufficiency, vomiting, diarrhea, shock, anesthesia, cardiac decompensation—See Table 2 for further data.
Total Proteins and Specific Gravity	(+)	Shock in dehydration, vomiting, diarrhea, excess sweating, burns, peritoneal injury, etc., myxedema, lymphogranuloma venereum, syphilis, Boeck's sarcoid, miliary tuberculosis, leprosy
	(-)	Nephrotic syndrome, shock due to blood and plasma loss, steatorrhea, chronic intestinal obstruction, hepatic disease, starvation, acute nephritis, cardiac decompensation
Albumin follows total protein		
Globulin and Fibrinogen	(+)	Multiple myeloma, kala azar, carcinomatosis, schistosomiasis, diphtheria immunization, various inflammatory states
Plasma Volume	(+)	Cardiac decompensation, polycythemia, certain types of chronic anemia, pregnancy
Plasma Volume	(-)	Shock, dehydration, renal insufficiency, chronic anemia, vomiting, diarrhea excess sweating

## MISCELLANEOUS BLOOD CONSTITUENTS AND SPECIAL TESTS

## IN HEALTH

Glucose	70-120 mg per 100 cc. (fasting)
Glucose Tolerance Test	(100 gm glucose by mouth) Maximum rise (in 90 minutes) less than 200 mg per 100 cc. Returns to normal in 120 minutes, below normal in 180 minutes. (50 cc. 50 per cent glucose i v) Blood sugar returns to 100 mg per 100 cc. in one hour
Insulin Tolerance Test	(0.1 U/kg i v) Glucose level decreases to half of fasting level in 20-30 minutes. Returns to fasting level in 90-120 minutes.
Lipase.	0.2-1.5 units (cc. N/20 NaOH to neutralize fatty acids released by 1 cc. of serum)
Amylase.	60-200 Somogyi units
Congo Red Test	More than 70 per cent of initial level after 30 minutes
Phosphatase—acid	0.5-3.5 King Armstrong units.
Phosphatase—alkaline	0.1-1.1 Shinowara Jones-Reinhart units. 4-13 King Armstrong units. 2-4 Bodansky units.
Creatinine	1.0-1.3 mg per 100 cc.
Creatine	(P) 0 (B) 1.5-7.0 mg per 100 cc.
Creatine Tolerance Test	(Oral—1.32 gm. creatine hydrate) Males—80 per cent retention. Females—70 per cent retention
"Hormonal Iodine	4.0-8.0 gamma per 100 cc.
17 Ketosteroids	Males—8-21 mg excreted in urine/24 hours Females—4-14 mg excreted in urine/24 hours
Chorionic Gonadotropin (Aschheim Zondek Test)	Negative
Milligrams per 100 cc.	
Nonprotein Nitrogen	25-35
Urea Nitrogen.	13-23
Uric Acid.	3-5
Ketone Acids	0.3-2.0
Lactic Acid	10-20
Pyruvic Acid (Bisulfite binding substances)	3.7-5.8
Phenols	1.7-3.2
Ammonia	0.1-0.3
Amino Acid Nitrogen	5-8
Guanidine	0.32-0.48
Vitamins	
Vitamin A	40-60 gamma per 100 cc.
Thiamine (B)	3.5-4.2 gamma per 100 cc.
Riboflavin (B)	35-45 gamma per 100 cc.
Nicotinic Acid	10-18 gamma/cc. red cells
Ascorbic Acid	0.5-1.5 mg per 100 cc.

## IN DISEASE

Glucose	
(+) Excitement, cold asphyxia, brain injury anesthesia, diabetes mellitus, insulin resistance Cushing's syndrome, adrenocortical tumor	
(-) Insulin sensitivity hyperinsulinism.	
Glucose Tolerance Test (oral)	
Hyperglycemic response—Diabetes mellitus, starvation hyperthyroidism, hyperpituitarism (acromegaly, etc.), myasthenia gravis, Cushing's syndrome.	



*Hypoglycemic response*—Hypothyroidism, hypopituitarism, Addison's disease, steatorrhea, diarrhea

Glucose Tolerance Test (intravenous)

*Hyperglycemic response*—As in oral

*Hypoglycemic response*—As in oral except that steatorrhea and diarrhea have no effect on curve

Insulin Tolerance Test

*Insulin resistance*—(delayed or absent fall)—Cushing's syndrome, hyperpituitarism (acromegaly, etc.) Insulin resistance of unknown etiology

*Hypoglycemic unresponsiveness*—(delayed or absent terminal rise)—Hyperinsulinism, Addison's disease, hypopituitarism

Lipase

(+) Pancreatitis, pancreatic neoplasm

Diastase

(+) Acute pancreatic disorders (trauma, pancreatitis, etc.), mumps

Congo Red Test

Less than 70 per cent of dye in blood after 30 minutes—amyloidosis, massive proteinuria

Phosphatase—acid

(+) Carcinoma of prostate

Phosphatase—alkaline

(+) Neoplasm of bone, Paget's disease of bone, fragilitas ossium, rickets, osteomalacia, hyperparathyroidism, biliary obstruction

Creatinine

(+) Renal insufficiency (except when acute or upon obstructive basis)

Creatine

(+) Renal insufficiency

Creatine Tolerance Test

Increased retention—Hypothyroidism, myotonia congenita

Decreased retention—Hyperthyroidism, myotonia atrophica, progressive muscular atrophy

"Hormonal" Iodine

(+) Hyperthyroidism, hyperpituitarism (acromegaly, etc.)

(-) Hypothyroidism, hypopituitarism

17-Ketosteroids

(+) Adrenal cortical carcinoma, adrenal cortical hyperplasia, testicular interstitial cell tumor

(-) Hypothyroidism, hypopituitarism, Addison's disease

Chorionic Gonadotropin—A-Z Test—positive

Pregnancy, hydatid mole, chorionepithelioma

Nonprotein Nitrogen and Urea Nitrogen

(+) Renal insufficiency, hyperthyroidism, shock, hemorrhage, fever, vomiting, diarrhea, cardiac decompensation, dehydration, pregnancy

Urea Nitrogen

(-) Starvation, diuresis, acute yellow atrophy

Uric Acid

(+) Renal insufficiency, gout, toxemia of pregnancy, leukemia

Ketone Acids

(+) Diabetes mellitus, starvation, alkalosis, vomiting

Lactic Acid

(+) Extreme exertion, cardiac decompensation, shock, diabetes mellitus

Pyruvic Acid

(+) Thiamine deficiency, cardiac decompensation, fever, diabetes mellitus, hyperthyroidism

Phenols

(+) Renal insufficiency, intestinal obstruction, pernicious anemia

Ammonia

(+) Renal insufficiency

Amino Acid Nitrogen

(+) Acute yellow atrophy, occasionally renal insufficiency, leukemia

(-) Nephrotic crisis

Guanidine

(+) Renal insufficiency

✓ Vitamins

(-) Dietary deficiency, fever, diarrhea, steatorrhea, hepatic disease, wasting disease.



## Icterus Index

(Up to 20—subclinical jaundice) Jaundice, carotinemia.

## Bilirubin (quantitative)

(+) Jaundice—indirect (+) in proportion to direct—hemolytic jaundice, direct (+) in proportion to indirect—obstructive, hepatotoxic jaundice (less marked disproportion)

## Cholesterol

(+) Hypothyroidism, biliary obstruction, cirrhosis, diabetes mellitus, nephrotic syndrome, renal insufficiency, hypercholesterolemic lipoidoses (xanthomatosis), cardiac disease

(–) Renal insufficiency, any extensive hepatic disease, hyperthyroidism, fever, cachexia, steatorrhea, anemia.

## Neutral Fat and Fatty Acids

(+) Hypothyroidism, anemia, diabetes mellitus, nephrotic syndrome

(–) Hyperthyroidism

## Lipoid Phosphorus

(+) Diabetes mellitus, nephrotic syndrome

(–) Anemia

\* The multiplicity of liver function tests renders complete tabulation impossible. Only the more reliable and commonly used procedures are listed.

## 4 RENAL FUNCTION TESTS

## IN HEALTH

## Clearance Tests

Inulin Clearance	Glomerular Filtration Rate (GFR)	Male	110–150 cc./min
Mannitol Clearance		Female	105–132 cc./min
Diodrast Clearance	Renal Plasma Flow (RPF)	Male	560–830 cc./min
P - aminohippurate Clearance		Female	490–700 cc./min

Filtration Fraction (FF) (equals GFR/RPF)

Male	17–21 per cent
Female	17–23 per cent
Standard	40–65 cc./min
Maximal	60–100 cc./min

Urea Clearance (Cu)

Male	300–450 mg./min
Female	250–350 mg./min
Male	43–59 mg./min
Female	33–51 mg./min

Maximal Glucose Reabsorptive Capacity (TmG)

Maximal Diodrast Excretory Capacity (TmD)

Phenolsulfonphthalein Excretion

Dilution-Concentration Test

40–60 per cent in first hour,
60–85 per cent in second hour
1 004–1 025

## IN DISEASE

GFR	(–)	Glomerulonephritis, nephrosclerosis, and other renal diseases, shock, anemia.
RPF	(+)	Fever, certain cases of acute diffuse glomerulonephritis.
RPF	(–)	Glomerulonephritis, nephrosclerosis, and other renal diseases, shock, anemia, apprehension, pressor drugs
FF	(+)	Essential hypertension, nephrosclerosis, pressor drugs
FF	(–)	Glomerulonephritis, fever, orthostasis, shock, anemia.
Cu	(+)	Fever, rising slope of diuresis curve, after protein meal.
Cu	(–)	Renal disease in which filtration is impaired, oliguria, shock, anemia
TmG, TmD	(–)	Tubular damage, (TmG also reduced by obliteration of glomeruli), any extensive renal disease
PSP	(+)	Fever, diuresis
PSP	(–)	Any extensive renal disease
Dilution, Concentration—Reduced range—tubular damage by any extensive renal disease		

## 5 THE CONSTITUENTS OF THE URINE

## IN HEALTH

	Grams per 24 Hours		Grams per 24 Hours
Water	1000-1500 cc.	Sodium	3 0-5 0
Total Solids.	55 0-70 0	Potassium	1 5-2 5
Specific Gravity	1 002-1 040	Calcium	0 1-0 3
pH	4 8-7 8	Magnesium	0 1-0 3
Urea	25 0-35 0	Iron	0 1-0 2
Creatine	0 0-0 06	Chloride	10 0-15 0
Creatinine	1 2-1 7	Iodine ( 'Hormonal ' ) adult	20-70 gamma
Amino Acids	0 2-0 4	child	20-35 gamma
Hippuric Acid	0 1-1 0	Sulfur—total.	2 0-3 4
Lactic Acid	20 0-80 0	Inorganic	1 7-2 7
Oxalic Acid	0 01-0 02	Ethereal	0 1-0 3
Uric Acid	0 2-0 8	Neutral	0 2-0 4
Purine Bases	0 01-0 06	Phosphate	2 5-3 5
Allantoin	0 005-0 015	Urobilin	0 01-0 13
Indican	0 005-0 01	Porphyrias	0-30 gamma
Phenols.	0 1-0 3	Thiamine.	30-300 gamma
Ammonia Nitrogen	0 5-1 0	Riboflavin	500-800 gamma
Total Reducing Substances	0 5-1 5	Nicotinic Acid	3-10 mg
Ketones	0 3-1 0	Ascorbic Acid	15-50 mg
		Hormones—See Table 2	

## IN DISEASE

Water	(+)	Diuresis, excess intake, diabetes insipidus, renal insufficiency
	(-)	Dehydration, shock, urinary obstruction, nephrotic syndrome
Total Solids and Specific Gravity	(+)	Dehydration, diabetes mellitus, cardiac decompensation
pH	(-)	Renal insufficiency, diabetes insipidus, diuresis.
	(+)	Diuresis, alkalosis, hyperventilation, after meals.
Urea	(-)	Oliguria, acidosis, shock, urinary infection
	(+)	Diuresis, high protein intake, starvation.
	(-)	Renal insufficiency, cardiac decompensation, shock, urinary ob- struction, oliguria, dehydration, low protein intake, acute yellow atrophy
Creatine	(+)	Hyperthyroidism, in childhood, starvation, cardiac decompensa- tion, myositis (trichiniasis, dermatomyositis, etc.) high crea- tine diet, progressive muscular dystrophy, myotonia atrophica, amyotonia congenita, myasthenia gravis, progressive muscular atrophy
Creatinine	(-)	Myotonia congenita.
	(+)	Familial periodic paralysis.
Amino Acids	(-)	Renal insufficiency myotonia congenita.
	(+)	Cystinuria, histidinuria, tyrosinuria.
Hippuric Acid	(-)	Renal insufficiency
Lactic Acid	(-)	Renal insufficiency any extensive hepatic disease.
	(+)	High carbohydrate diet, exercise, anoxemia, pneumonia, dysp- nea, anesthesia.
Oxalic Acid	(+)	Increased dietary intake (rhubarb, etc.)
Uric Acid	(+)	Increased purine intake, exercise, pregnancy labor, during acute episode of gout, toxemia of pregnancy
Purine Bases	(-)	Starvation gout (between acute attacks) renal insufficiency
Allantoin	(+)	Increased purine intake.
Phenols	(-)	Renal insufficiency
	(+)	Drugs, intestinal obstruction, renal insufficiency

Ammonia	(+)	Pregnancy, toxemia of pregnancy, vomiting, diarrhea, dehydration, acidosis, urinary infection by urea-splitting organisms
	(-)	Renal insufficiency
Total Reducing Substances	(+)	Glycosuria in diabetes mellitus, Cushing's syndrome, renal diabetes, chronic or acute pancreatitis, pernicious anemia, pregnancy, severe pyogenic infection, pentosuria, lactosuria
Ketones	(+)	Alkalosis, starvation, prolonged vomiting, diarrhea, diabetes mellitus
Sodium	(+)	Diuresis, renal insufficiency, Addison's disease, after meals
	(-)	Sweating, renal insufficiency, diarrhea, vomiting, dehydration, anesthesia, pneumonia, diabetes mellitus, Cushing's syndrome, cardiac decompensation, nephrotic syndrome
Potassium	(+)	Diuresis, dietary increase, drugs, renal insufficiency, family periodic paralysis, Cushing's syndrome
	(-)	Addison's disease, renal insufficiency, dehydration
Calcium	(+)	Hyperparathyroidism, excess vitamin D intake, diuresis, acidosis
	(-)	Renal insufficiency, hypoparathyroidism, hyperthyroidism, steatorrhea, diarrhea, vitamin D deficiency
Magnesium	(+)	Acidosis
	(-)	Hyperphosphatemia, high fat intake, alkalosis, hyperparathyroidism
Iron	(+)	Hemachromatosis, hematuria, hemoglobinuria
Chloride	(+)	Renal insufficiency, diuresis, high chloride intake, acidosis, Addison's disease
	(-)	Starvation, dehydration, diarrhea, vomiting, after meals, sweating, prolonged hyperventilation, anesthesia, alkalosis, fever, cardiac decompensation, renal insufficiency, pernicious anemia, Cushing's syndrome
Iodine	(+)	Hyperthyroidism
	(-)	Hypothyroidism
Sulfur	(+)	Cystinuria, acute yellow atrophy, melanuria
Ethereal Fraction	(+)	Phenol ingestion, intestinal obstruction
Phosphate	(+)	Acidosis, hyperparathyroidism, hyperthyroidism, vomiting
	(-)	Hyperinsulinism, renal insufficiency, hypoparathyroidism, hypothyroidism, pregnancy, anesthesia
Urinary Pigments—Porphyrins	(+)	Acute porphyria, excess intake of veronal, sulfonal, etc., congenital porphyria, hepatic disease, pernicious anemia, hemolytic anemia, hemoglobinuria
Vitamin	(-)	Renal insufficiency and dietary deficiency

## 6 RESPIRATORY DATA

## IN HEALTH

## Blood Gases

*Arterial*

Oxygen Content	16-20 vol per cent	pO <sub>2</sub> 95-100 mm Hg
Oxygen Hemoglobin Capacity	17-21 vol per cent	
Oxygen Content/Oxygen Capacity	95-97 4 per cent	
Carbon Dioxide Content	49 6-54 4 vol per cent	pCO <sub>2</sub> 40 2-47 2 mm Hg
Carbon Dioxide Content (T40)	48 3-52 9 vol per cent	
Carbon Monoxide	0 1-0 5 vol. per cent	

*Venous*

Oxygen Content	11 0-16 9 vol per cent	pO <sub>2</sub> 30-50 mm Hg
Oxygen Content/Oxygen Capacity	60-35 per cent	
Carbon Dioxide Content.	55-74 vol per cent	pCO <sub>2</sub> 37-58 mm Hg
Carbon Dioxide Content (T40)	43 3-55 9 vol. per cent	

<b>Respiratory Gases</b>	
Alveolar Air	
Oxygen	13.5-15.5 vol. per cent $pO_2$ 95-110 mm. Hg
Carbon Dioxide	5.3-6.3 vol per cent $pCO_2$ 38-45 mm. Hg
Carbon Dioxide Output	87-117 cc./min /square meter surface area
Oxygen Absorption	120-145 cc /min /square meter surface area
Ventilation	2.5-3.9 L./min /square meter surface area
<b>Vital Capacity</b>	
Male	4000-5700 cc.
Female	2300-3900 cc.
Basal Metabolic Rate	$\pm$ 10 per cent of mean standard

## IN DISEASE

*Arterial*

## Oxygen Content

- (+) Polycythemia.
- (-) Anemias, high altitude, pulmonary edema, emphysema, bronchial asthma, pneumonia, pneumothorax, congenital heart disease.

## Oxygen Capacity

- (+) Polycythemia.
- (-) Anemia, carbon monoxide poisoning, methemoglobinemia

## Oxygen Saturation

- (-) High altitude, pneumonia, respiratory obstruction, pulmonary edema, congenital heart disease.

## Carbon Dioxide Content

- (+) Pneumonia, respiratory obstruction, pulmonary edema, congenital heart disease, emphysema. [See Table 1— $HCO_3$  (+)]
- (-) Hyperventilation. [See Table 1— $HCO_3$  (-)]

*Venous*

## Oxygen Content and Oxygen Saturation

- (+) Hyperventilation fever hyperthyroidism
- (-) High altitude, pneumonia, respiratory obstruction, pulmonary edema, congenital heart disease, cardiac decompensation, anemia, carbon monoxide poisoning methemoglobinemia, shock, cold, exercise.

## Carbon Dioxide Content

- (+) (See arterial carbon dioxide content) cardiac decompensation shock, cold
- (-) (See arterial carbon dioxide content.)

*Respiratory Cases*

## Alveolar Oxygen

- (-) High altitude.

## Alveolar Carbon Dioxide

- (-) Hyperventilation.

## Carbon Dioxide Output

- (+) Increased R. Q. or metabolism, acidosis.
- (-) Alkalosis, decreased R.Q. and metabolism.

## Oxygen Absorption

- (+) Increased total metabolism, see B.M.R.
- (-) Decreased total metabolism.

## Ventilation

- (+) Exercise fever acidosis, post-encephalitic and hysteric hyperventilation head injury high altitude
- (-) Alkalosis, morphinism.

*Vital Capacity*

- (+) Orthostasis.
- (-) Cardiac decompensation pulmonary edema, pneumothorax, hydrothorax and other extensive intrathoracic processes, respiratory obstruction

B.M.R. (+) Excitement, psychoneurosis, fever hyperthyroidism caffeine, polycythemia, leukemias, cardiac decompensation.

(-) Starvation hypothyroidism, shock, edema, hypopituitarism.

## 7 HEMATOLOGICAL DATA

## IN HEALTH

*Blood Cytology*

Total leukocytes		7,000-10,000 cells/cu. mm
Myelocytes		0
Juvenile neutrophils		3-5 per cent
Segmented neutrophils		54-62 per cent
Eosinophils		1-3 per cent
Basophils		0-1 per cent
Lymphocytes		25-33 per cent
Monocytes		3-7 per cent
Platelets		250 000-400,000/cu mm
Red blood cells	male	4,600,000-6,200,000 cells/cu. mm
	female	4,200,000-5,400,000 cells/cu mm
Reticulocytes		0-2 per cent

Hemoglobin	male	14 0-18 0 gm per 100 cc.
	female	12 0-16 0 gm per 100 cc.
Volume, packed cells (hematocrit)		
	male	40 0-52 0 cc. per 100 cc.
	female	37 0-47 0 cc. per 100 cc.
Mean Corpuscular Volume		82 0-92 0 c $\mu$
Mean Corpuscular Hemoglobin		27 0-31 0 $\gamma\gamma$
Mean Corpuscular Hemoglobin Concentration		32 0-36 0 per cent
Mean Corpuscular Diameter		7 2-7 8 $\mu$
Erythrocyte Fragility Test		
	Slight hemolysis	in 0 45-0 39 per cent sodium chloride
	Marked hemolysis	in 0 42-0 36 per cent sodium chloride
	Complete hemolysis	in 0 33-0 30 per cent sodium chloride
Erythrocyte Sedimentation Rate		
	Wintrobe	0-15 mm /hour
	Westergren—male	1-3 mm /hour
		3-7 mm./hour
	female	0 1-0 4 mm./min
	Rourke-Ernstene	
Bleeding Time		1-3 min
Coagulation Time		2-10 min
Retraction Time of Blood Clot		1 hour
Prothrombin Time (Quick)		12-14 seconds (60-120 per cent of normal)
Capillary Fragility Test		10-15 petechiae/sq in on forearm, 5 cm below elbow, after 10 min cuff pressure on arm at 90 mm Hg

*Bone Marrow Cytology*

## Per Cent

Granulopoietic Series	
Myeloblasts	0 3-5 0
Promyelocytes	1 0-8 0
Myelocytes—neutrophilic	5 0-19 0
	eosinophilic
	0 5-3 0
	basophilic
	0 0-0 5
Metamyelocytes ("juvenile forms")	13 0-32 0
Polymorphonuclear neutrophils	7 0-30 0
	eosinophils
	0 5-4 0
	basophils
	0 0-0 7
Lymphocytes	3 0-17 0
Plasma cells	0 0-2 0
Monocytes	0 5-5 0
Reticulum cells	0 2-2 0
Megakaryocytes	0 03-3 0

# LABORATORY FINDINGS IN BLOOD AND URINE

1325

Erythropoietic Series  
Pronormoblasts (macroblasts)  
Normoblasts (basophilic, polychromatophilic)  
Megaloblasts and other non nucleated red cell forms present in varying degrees.

1 0-8 0

7 0-32 0

## IN DISEASE

Total Leukocytes (usu  
ally neutrophils) (+) Acute infections, hemorrhage at birth labor vomiting poi  
sonings, renal insufficiency diabetes mellitus, gout, leu  
kemia.

(-) Certain infections (typhoid virus and protozoal infections)  
overwhelming infection or toxemia cachexia, Banti's  
syndrome.  
(+) Allergy, skin diseases, parasitic diseases, scarlet fever,  
chorea, pernicious anemia, myelocytic leukemia.

(+) Chronic myelocytic leukemia, Hodgkin's disease, chicken  
pox, smallpox.  
(+) Certain infections (pertussis, infectious mononucleosis, ex  
anthema tuberculosis) lymphocytic leukemia.

(+) Certain infections (tuberculosis, typhus, many  
ricketsial and protozoal [malaria, trypanosomiasis] infec  
tions), monocytic leukemia, tetrachlorethane poisoning  
kala azar  
(+) Appear in leukemias particularly myelocytic leukemia.  
(+) Rheumatic fever acute suppuration, fractures, hemorrhage  
chronic myelocytic leukemia, Hodgkin's disease, eryth  
remia.

(-) 'Primary' thrombocytopenic purpura, certain chemicals  
(arsenicals, sodium benzol, gold salts), leukemias, severe  
anemias and infections, Banti's and Gaucher's diseases.  
(+) Appear in hemolytic anemia pernicious anemia during  
treatment.  
(+) MCHC (N)

Macrocytic anemia, pernicious anemia, carcinoma of stom  
ach neoplastic invasion of bone marrow (myelophthisic  
anemia) pellagra, sprue after gastrectomy fish tape  
worm infestation  
Normocytic anemia, hemorrhage, hemolytic anemias, aplas  
tic anemia.

(+) Microcytic, hypochromic anemia, iron deficiency "Medit  
erranean anemia."  
(-) Congenital hemolytic anemia.  
(-) Hypochromic anemia, Mediterranean anemia, polycy  
themia vera.

(+) Acute general infections localized suppurative processes,  
severe chronic infection extensive neoplasm, myocardial  
infarction, late pregnancy  
Thrombocytopenic purpura, hereditary hemorrhagic  
diathesis.

(+) Severe liver disease, vitamin K deficiency leukemias.  
(+) Scurvy scarlet fever measles, influenza, chronic renal dis  
ease, leukemia.

(+) Pernicious anemia, polycythemia, Hodgkin's disease  
agranulocytosis.

Eosinophils

Basophils

Lymphocytes

Monocytes

Myelocytes

Platelets

reticulocytes

Hct., RBC (-) MCV MCH

Hct. RBC (-) MCV MCH

Hct., RBC, MCV MCH, MCHC (N)

Erythrocyte Fragility

Sedimentation Rate

Bleeding Time (+) Coagulation Time (N)

Bleeding Time Prothrombin Time, Coagulation Time

Bleeding Time (N) Coagulation Time (+)

Capillary Fragility

Bone Marrow

Myeloblasts



Myelocytes	(+)	Myelocytic leukemia, pernicious anemia, agranulocytosis
Metamyelocytes	(+)	Agranulocytosis
Polymorphonuclear Granulocytes	(+)	Leukemias
	(-)	Pernicious anemia.
Lymphocytes	(+)	Lymphatic leukemia
Plasma cells	(-)	Multiple myeloma.
Monocytes and Reticulum Cells	(+)	Monocytic leukemia.
Megakaryocytes	(+)	Polycythemia vera.
Pronormoblasts	(+)	Iron deficiency
	(-)	Pernicious anemia
Normoblasts	(+)	Iron deficiency, polycythemia vera
	(-)	Pernicious anemia, aplastic anemia
Megaloblasts	(+)	Markedly—pernicious anemia

## BIBLIOGRAPHY

- 1 Bodansky, M and Bodansky, O Biochemistry of Disease. New York, Macmillan Co., 1940
- 2 Cournand, A and Richards, D W, Jr Pulmonary Insufficiency I Discussion of a Physiological Classification and Presentation of Clinical Tests *Am Rev Tuberc.*, 44 26, 1941
- 3 Dameshek, W Biopsy of the Sternal Bone Marrow *Am J M Sc*, 190 617, 1935
- 4 Fraser, R, Albright, F and Smith, P H The Value of the Glucose Tolerance Test, the Insulin Tolerance Test, and the Glucose-Insulin Tolerance Test in the Diagnosis of Endocrinologic Disorders of Glucose Metabolism *J Clin Endocrinol*, 1 297, 1941
- 5 Harrow, B Textbook of Biochemistry, 3rd ed Philadelphia, W B Saunders Co., 1944
- 6 Lichtman, S S Diseases of the Liver, Gallbladder and Bile Ducts Philadelphia, Lea & Febiger, 1942
- 7 Myers, V C and Muntwyler, E. Chemical Changes in the Blood and Their Clinical Significance *Physiol Rev*, 20 1, 1940
- 8 Peters, J P Water Exchange *Physiol Rev*, 24 491, 1944
- 9 Peters, J P and Van Slyke, D D Quantitative Clinical Chemistry I Interpretations II Methods Baltimore, Williams & Wilkins Co., 1932
- 10 Ross, J F Common Laboratory Aids to Diagnosis and Treatment. *M CLIN NORTH AMERICA*, 26 1391 (Sept.) 1942
- 11 Salter, W T Clinical Blood Chemistry in General Practice New England J Med., 224 19, 1941
- 12 Shuman, H H and Jeghers, H The Value of Routine Blood Protein Determinations *New England J Med*, 222 335, 1940
- 13 Simmons, J S and Gentzkow, C J Laboratory Methods of the United States Army, 5th ed Philadelphia, Lea & Febiger, 1944
- 14 Smith, H W et al The William Henry Welch Lectures II The Application of Saturation Methods to the Study of Glomerular and Tubular Function in the Human Kidney *J Mt Sinai Hosp.*, 10 59, 1943
- 15 Talbot, N B and Butler, A. M Urinary 17-Ketosteroid Assays in Clinical Medicine *J Clin Endocrinol.*, 2 724, 1942
- 16 Todd, J C and Sanford, A H Clinical Diagnosis by Laboratory Methods, 10th ed Philadelphia, W B Saunders Co., 1944
- 17 Wintrobe, M M Clinical Hematology Philadelphia, Lea & Febiger, 1942

# CUMULATIVE INDEX

- Abortion early, progesterone in *Jan* 264  
 emergency aspects, *July* 853 856  
 Abruptio placentae, *July* 855 857  
 Abscess, intracranial, emergency treatment, *July*, 895  
 of lung emergency aspects *July* 841  
 surgical indications and treatment *Sept.*, 1288  
 Achlorhydria, acid therapy, *March* 426  
 Acidosis in chronic diffuse glomerulo nephritis, *Sept.*, 1193  
 Acne vulgaris, hormone therapy *Sept* 1111  
 Actinomyces, *March*, 338  
 Adams-Stokes syndrome, *Sept.*, 157  
 Addison's disease, *July* 1016  
 desoxycorticosterone acetate in *March*, 435  
 Adenoma of bronchus, hemoptysis in *July* 843  
 parathyroid *March* 390-393  
 Adrenal cortex disturbances, *July*, 1016  
 medulla disturbances *July* 1016  
 Agglutination test for brucellosis, *March* 353  
 Akinetic seizures, *Sept.*, 1117 1123  
 Albumin bovine, *Sept.*, 1091  
 human, *March* 433 *Sept* 1086  
 Albuminocytologic dissociation in acute infectious radiculoneuritis, *Jan* 1  
 Alcohol injections for facial pain, *Jan* 77  
 Alcoholism criminal responsibility and *Jan* 212  
 Alloxan in production of diabetes *March*, 436  
 Aluminum hydroxide in hypoparathyroidism *March* 435  
 powder in silicosis, *March* 437  
 Amebiasis, postwar problem of *July* 906  
 Amenorrhea, hormone therapy *Jan* 258 260 263  
 Amigen, *March* 433  
 Amino acids parenteral uses, *March* 433  
 Aminophylline in asthma in children *July* 867  
 Analgesics in convalescence *Sept.*, 1212  
 Anaphylactoid purpura *July* 880  
 Androgen therapy, advances in *March* 436  
 in menstrual disorders *Jan* 265  
 Anemia, hemolytic acute acquired *May* 695  
 in carcinoma of colon *July* 958  
 Anemia in chronic diffuse glomerulo nephritis *Sept* 1198  
 Lederer's, *May*, 702  
 pernicious *Jan* 229  
 clinical types, *Jan.*, 230  
 liver therapy *Jan.*, 242  
 posterolateral sclerosis in management *Jan* 245  
 severe electrocardiogram in *May* 608  
 suspension of discarded erythrocytes in *March* 432  
 Anemias, macrocytic, *Jan.*, 246  
 Anesthesia general curare in *March* 423  
 local new agents *March* 419  
 surgical electrocardiogram in *May* 614  
 Angina pectoris, anoxemia test, *May* 616  
 differential diagnosis, *March* 513  
 testosterone in *March* 425  
 Ankle clonus in pyramidal tract lesions *Jan* 56  
 Anoxemia test in angina pectoris *May*, 616  
 Anthrax, penicillin in *July* 835  
 Antibiotics in dermatology *Sept.*, 1107  
 Anuria in infants and children *July* 874  
 Anxiety later fate of *May* 747  
 neurosis, in combat crews *May* 731  
 Aorta aneurysm electrocardiograms in *May* 605  
 coarctation electrocardiogram in *May*, 605 606  
 Appendicitis, acute, in children *July* 879  
 chronic simulating peptic ulcer *May* 629  
 Army Air Forces, rehabilitation in, *May*, 715  
 rheumatic fever in convalescent care *May* 765  
 Army fatigue and exhaustion states in *May* 771  
 reconditioning programs *May* 788  
 Arrhythmias, *Sept.*, 1154  
 digitalis in *March* 531  
 quinidine in *Jan.*, 216  
 Arthralgias, *Sept.*, 1271  
 Arthritic conditions common, treatment *Sept* 1269  
 Arthritis, *Sept.*, 1276  
 hypertrophic *Sept.*, 1278  
 physical medicine in *May* 790  
 rheumatoid *Sept.*, 1277  
 etiology environmental factors *May* 566

- Arthritis, rheumatoid, gold salts therapy, *Sept*, 1277  
 neostigmine in, *March*, 423  
 Aspiration biopsy of liver, *March*, 365  
 Aspirin, blood coagulation and, *March*, 430  
 Asthma, bronchial, complications, unusual, *March*, 456  
 military service and, *March*, 455  
 recent advances, *March*, 453  
 treatment, *March*, 458, 461  
 emergency aspects, *July*, 843  
 in children, *July*, 866  
 with heart disease in children, *July*, 871  
 Atelectasis, massive, emergency aspects, *July*, 844  
 Auricular fibrillation, *Sept*, 1157  
 digitalis in, *March*, 532  
 quinidine in, *Jan*, 217  
 flutter, *Sept*, 1156  
 digitalis in, *March*, 532  
 quinidine in, *Jan*, 223  
 tachycardia, paroxysmal, *Sept*, 1154  
 Axillary nerve injuries, *Jan*, 23  
 BABINSKI sign in pyramidal tract lesions, *Jan*, 47  
 Bacillary dysentery, postwar problem of, *July*, 905  
 Bacillus coli meningitis, *Sept*, 1268  
 Back strain, *May*, 568  
 Barbiturates in convalescence, *Sept*, 1213  
 in war psychoses, *March*, 418  
 Basophilism, pituitary, *July*, 1011  
 Baths in skin disease, *Sept*, 1096  
 Bed rest in convalescence, undesirable effects, *May*, 720, 748, 809  
 Behavior clinic of criminal court, *Jan*, 202  
 Benzedrine in epilepsy, *Sept*, 1122  
 in prevention of motion sickness, *March*, 418  
 Beriberi, diet in, *May*, 803  
 Biopsy, endometrial, *Jan*, 252  
 in lymphogranuloma venereum, *May*, 678  
 liver, by aspiration, *March*, 365  
 Bladder atony, furmethide in, *March*, 421  
 female, functional disturbances, management, *Sept*, 1200  
 neck obstruction, fibrous, *Sept*, 1208  
 Blastomycosis, *March*, 334  
 Blood coagulation, drugs influencing, *March*, 430  
 derivatives, indications and uses, *Sept*, 1069  
 donors, universal (Group O), *Sept*, 1077  
 grouping technic, *Aug*, 1078  
 indications and uses, *Sept*, 1069  
 laboratory findings, in health and disease, *Sept*, 1314  
 Blood loss, acute, electrocardiogram in, *May*, 613  
 storage, media for, *Aug*, 1077  
 substitutes, indications and uses, *Sept*, 1069, 1091  
 uses, physiologic background, *Sept*, 1069  
 vessels, peripheral, effect of cigarette smoking in, *July*, 949  
 whole, use of, *Sept*, 1075  
 Bone marrow cytology, *Sept*, 1324  
 Bones, lesions, in hyperparathyroidism, *March*, 394, 396  
 Brachial plexus injuries, *Jan*, 19  
 Brain tumor in children, *July*, 892  
 Brewers' yeast, dosages, *Sept*, 1303  
 Bromides in convalescence, *Sept*, 1214  
 in epilepsy, *Sept*, 1120  
 Bromsahzol, *March*, 419  
 Bromsulfalein test of liver function, *July*, 976  
 Bronchial asthma, recent advances, *March*, 453  
 Bronchiectasis, emergency aspects, *July*, 840  
 surgical indications and treatment, *Sept*, 1284  
 Broncholithiasis, emergency aspects, *July*, 842  
 Bronchopneumonia in infants and children, *July*, 869  
 penicillin in case report, *May*, 580  
 Bronchus, adenoma of, hemoptysis in, *July*, 843  
 Brucellin, *March*, 359  
 Brucellosis, *March*, 343  
 penicillin failure in, *May*, 586  
 Buboes, inguinal, in lymphogranuloma venereum, *May*, 668  
 Bubonoli, *May*, 669, 670  
 Burns, infection due to, penicillin in, *July*, 836  
 shock in, sodium lactate in, *March*, 438  
 CAFFEINE in epilepsy, *Sept*, 1122  
 Calcium in dermatology, *Sept*, 1104  
 Candida albicans, infections with, *March*, 323  
 Carbon dioxide in bronchial asthma, *March*, 459  
 Carbuncles, penicillin in, *July*, 836  
 Carcinoma of colon, proximal portion, iron deficiency and anemia associated with, *July*, 958  
 of lung, emergency aspects, *July*, 842  
 primary surgical indications and treatment, *Sept*, 1282  
 of prostate, estrogen therapy, *March*, 435  
 of stomach, diagnosis, *March*, 489  
 gastroscopy in, *March*, 499  
 Caruncle of urethra, *July*, 1007

- Cataplexy, potassium chloride in, *March* 422
- Catarh, gastric, with peptic ulcer, *May* 628
- Catalgalia, *Jan.*, 13
- Cauterization of cervix in chronic cervicitis, *July* 1002
- Cavernostomy in tuberculous, *March* 450
- Cavernous sinus thrombosis, emergency treatment, *July* 834
- Cedilanid, *March* 424 529
- Cellulitis, penicillin in *May*, 85- *July* 836
- Cerebral palsies of children rehabilitation in, *May* 792 819
- thrombosis in children, *July* 894
- Cervicitis, chronic, *July*, 998
- Chaddock's sign in pyramidal tract lesions, *Jan.*, 50
- Chemotherapy in brucellosis, *March*, 357
- in lymphogranuloma venereum, *May* 682
- in tuberculosis *March* 445 *July* 918
- in urinary tract infections, *May*, 574, 575
- Children, cardiac emergencies in, *July* 871
- gastro-intestinal emergencies in, *July* 878
- neurologic emergencies in, *July* 886
- respiratory tract emergencies in, *July* 864
- urinary tract emergencies in, *July* 874
- Chloral hydrate in convalescence *Sept.*, 1214
- Cholera, postwar problem of *July* 901
- Cholesterothorax, *March* 507 510
- Choline in cirrhosis of liver *March* 429 484
- Chordotomy for intractable pain, *Jan.*, 98
- Choriomeningitis, lymphocytic, benign, *Jan.*, 36
- Chromoblastomycosis, *March* 336
- Chylothorax, *March* 506 510
- Cigarette smoking, effect on heart and peripheral blood vessels, *July* 949
- Circus movement, *Jan.*, 216
- Cirrhosis of liver correlation of composite liver function study with liver biopsy *March* 363
- diagnosis *March* 480
- dietary treatment, *March* 276, 429 484 485 *May* 655
- etiology, *March* 273 479
- lipotropic substances in *March* 428 484, *May* 658
- nutritional deficiencies as basis *May* 655
- symptoms and signs, *March* 275
- treatment, recent advances, *March* 273 479
- Cirrhosis of liver with clinical features of xanthomatous biliary cirrhosis but with confirmation at biopsy *July* 1054
- Clawed hand in ulnar nerve injury *Jan.*, 15
- Clonus in pyramidal tract lesions, *Jan.*, 56
- Coccidioidin, *March* 334
- Coccidioidomycosis, *March* 332
- postwar problem of *July* 907
- Cold, common, propadrine hydrochloride in *March* 420
- Colic in infants *July* 8 8
- Colitis, chronic ulcerative, sulfathalidine in *March* 427
- Colon diverticulitis and diverticulosis clinical study *May* 639
- proximal portion, carcinoma of iron deficiency and anemia associated with *July* 958
- Coma, diabetic, *July* 893
- in children, emergency treatment *July* 892
- Communicable diseases, common, active immunization against, *Sept.*, 1238
- Complement fixation test in lymphogranuloma venereum *May* 678
- Convalescence bed rest in, undesirable effects, *May* 720 748, 809
- in home, rehabilitation problems, *May* 818
- in hospital, rehabilitation problems, *May* 808
- management of patient, *Sept.*, 1210
- Convalescent care of rheumatic fever in Army Air Forces, *May* 765
- hospital, Army Air Forces, role of *May* 721
- serum, *Aug.*, 1035
- training program, Army Air Forces, *May* 716
- ward need for *May* 812
- Convulsions in children, emergency treatment, *July* 886
- Convulsive shock therapy in psychoses, *Sept.*, 1232
- Coronary thrombosis, *Sept.*, 1160
- electrocardiograms in, *May* 598
- pain of differential diagnosis, *March* 513
- quinidine in, *Jan.*, 22,
- restriction of activity in and extent of myocardial infarction, *March* 405
- Creams dermatologic, *Sept.*, 1100
- protective *Sept.*, 1103
- Criminal responsibility epilepsy and, *Jan.*, 212
- insanity and *Jan.*, 195
- mental retardation and, *Jan.*, 203
- Croup *July* 864

- Cryptococcosis, *March*, 335  
 Curare, new uses, *March*, 423  
     test for myasthenia gravis, *Jan*, 129  
 Cushing's syndrome, *July*, 1011, *Sept*, 1224  
 Cyst, suprasellar, obesity with, *Sept*, 1222  
 Cystic disease of lung, emergency aspects, *July*, 845  
 Cystine in liver disease, *March*, 429  
 Cystitis, acute, in female, *Sept*, 1202  
     chronic interstitial, *Sept*, 1205  
  
 D-DESOXYEPHEDRINE hydrochloride, *March*, 420  
 Deafness, conductive, relation to lymphoid hyperplasia of endometrium and x-ray therapy, *Sept*, 1251  
 Deficiency diseases, arthralgia due to, *Sept*, 1271  
     rehabilitation problems, *May*, 794  
 Dementia praecox, *Jan*, 148  
 Demerol, *March*, 417  
     in convalescence, *Sept*, 1212  
 Dengue fever, postwar problem of, *July*, 900  
 Depression in combat crews, *May*, 732  
     in returned soldiers, *May*, 736  
 Dermatitis, acute, emergency aspects, *July*, 833  
 Dermatology, nonsurgical emergencies encountered in, *July*, 833  
 Dermatophytosis, *March*, 323  
     treatment, *March*, 326  
 Dermatoses, common, treatment, *Sept*, 1095  
 Desoxycorticosterone acetate in Addison's disease, *March*, 435  
 Diabetes insipidus, *July*, 1009  
     mellitus, *July*, 1014  
     globin insulin in, *March*, 436  
 Diabetic coma, *July*, 893  
     electrocardiogram in, *May*, 608  
 Diarrhea, acute, in infants and children, *July*, 882  
 Diasone in tuberculosis, *March*, 447, 448, *July*, 921  
 Dichlorophenarsine hydrochloride in syphilis, *March*, 438  
 Dicoumarol in prevention of embolism and thrombosis, *March*, 430, 431, *July*, 840, 929  
 Dienoestrol, *March*, 435  
 Diet in acidosis of chronic diffuse glomerulonephritis, *Sept*, 1196  
     in cirrhosis of liver, *March*, 276, 427, 484, *May*, 655  
     in convalescence, *Sept*, 1215  
     in epilepsy, *Sept*, 1119  
     in nephrosis, *Sept*, 1186  
     in nutritional deficiencies, *May*, 799-802  
     in obesity in children, *Sept*, 1227  
  
 Diet in peptic ulcer, fundamental importance, in Army hospital, *May*, 706  
     in pernicious anemia, *Jan*, 244  
     in recurrent peptic ulcer, *Sept*, 1167  
     in rehabilitation, *May*, 794  
 Digiland, *March*, 423  
 Digitaline native, *March*, 423  
 Digitalis, blood-clotting and, *March*, 431  
     effects on electrocardiogram, *May*, 609  
     in arrhythmias, *March*, 531  
     in heart failure, *March*, 524  
     preparations and uses, *March*, 423, 524  
 Digitoxin, *March*, 423  
 Digoxin, *March*, 424, 529  
 Dihydrotachysterol in hyperparathyroidism, *March*, 402  
 Dilantin sodium in bronchial asthma, *March*, 459  
 Dilaudid in convalescence, *Sept*, 1212  
 Diphtheria, immunization, *Sept*, 1240  
     laryngeal, *July*, 866  
 Diuresis in nephrosis, *Sept*, 1187  
 Diuretics, new, *March*, 424  
 Diverticulitis of colon, *May*, 639  
 Diverticulosis of colon, clinical study, *May*, 639  
 Diverticulum, urethral, *July*, 1008  
 Drop wrist in radial nerve injury, *Jan*, 10  
 Dye excretion tests of liver function, *July*, 976  
 Dysentery, amebic, postwar problem of, *July*, 906  
     bacillary, postwar problem of, *July*, 905  
     sulfasuxidine in, *March*, 426  
     sulfathalidine in, *March*, 426  
     sulfonamides in, *Sept*, 1311  
 Dysmenorrhea, hormone therapy, *Jan*, 259, 262, 265, 267  
 Dyspnea, pulmonary disturbances causing, emergency aspects, *July*, 843  
  
 ECLAMPSIA, *July*, 852  
 Ectopic pregnancy, ruptured, *July*, 854, 856  
 Edema of lung, acute, emergency aspects, *July*, 837  
 Educational retraining in Army Air Forces, *May*, 721  
 Electrocardiography, uses in medicine, *May*, 590  
     ventricular gradient in, *March*, 464  
 Electrodiagnosis in peripheral nerve injuries, *Jan*, 23  
 Electroencephalography in epilepsy, *Sept*, 1118, 1126  
 Electroschock therapy in psychoses, *Sept*, 1232  
     with insomnia, *Jan*, 192  
     outpatient, in psychiatric disorders, *Jan*, 165

- Embolism prevention, dicoumarol in *March* 430, 431, *July* 840 929  
 heparin in *March*, 431 *July* 933  
 pulmonary, emergency aspects *July* 839  
 prevention exercises for, *May* 789  
 Emergencies, medical, symposium on *July* 833  
 Emotional states, arthralgia due to *Sept* 1271  
 Emotions, neuropsychology of, *May* 744  
 Empyema, pyogenic *March*, 507, 510  
 Emulsions, *Sept.*, 1099  
 Encephalitis, acute, emergency treatment *July*, 895  
 Encephalo myelo-radikuloneuritis, acute, *Jan.*, 1  
 Endocarditis, bacterial, subacute non hemolytic streptococcus, treatment with penicillin *Sept.*, 1229  
 penicillin in *May*, 583  
 brucella, *March* 348  
 subacute bacterial, therapeutics, *March* 425  
 Endocrine glands real versus supposed disturbances, *July*, 1009  
 system, therapeutics *March*, 433  
 therapy in dermatology *Sept.*, 1111  
 in menstrual disorders, *Jan.*, 251  
 Endometrial biopsy *Jan* 252  
 Enuresis, ephedrine in *March*, 420  
 Ephedrine in asthma in children *July* 867  
 in enuresis, *March* 420  
 in myasthenia gravis, *Jan.*, 134 *March* 421  
 Epidermatophytosis, *March* 323  
 Epilepsy, criminal responsibility and *Jan.*, 212  
 diagnosis, *Sept* 1114  
 electrocardiogram in *May* 608  
 electroencephalography in *Sept.*, 1118 1126  
 glutamic acid in *March* 418  
 treatment, *Sept.*, 1114 1119  
 types of seizures, *Sept.*, 1115  
 Epinephrine in asthma in children *July*, 867  
 Erb's paralysis in brachial plexus injuries, *Jan.*, 19  
 Erysipelas, penicillin in *July* 836  
 Erysipeloid penicillin in *July* 836  
 Erythrocytes resuspended uses of *March* 432 *Sept.*, 1077  
 sedimentation rate, clinical significance, *July* 937  
 Esthlmene, *May* 670  
 Estrogen therapy in menstrual disorders *Jan.*, 239  
 in prostatic cancer *March* 435  
 new products, *March* 435  
 Ether in oil intramuscularly, in bronchial asthma, *March* 459  
 Ethinyl estradiol *March*, 435  
 Exercises in pulmonary embolism prevention *May*, 789  
 therapeutic in convalescence *May* 787 810  
 Exhaustion states in Army and in industry *May* 771  
 Expectorants in bronchial asthma, *March*, 438  
 Extrasystoles, quinidine in *Jan.*, 227  
 Eye signs in brucellosis, *March* 347  
 FACIAL pain, neoplasia as cause *Jan* 91  
 relief of *Jan.*, 73  
 symptomatic, *Jan.*, 87  
 Fasciculation neostigmine in *March* 422  
 Fatigue, arthralgia due to *Sept.*, 1271  
 "operational" *May* 729  
 states in Army and in industry, *May* 771  
 Fats, plasma, in liver disease, *July*, 979  
 Fear electrocardiographic changes induced by *May*, 618  
 Feeble-mindedness, criminal responsibility and, *Jan* 208  
 Feet dermatophytosis of, *March*, 323  
 Femoral nerve injuries, *Jan.*, 23  
 Ferrous carbonate in facial pain, *Jan.*, 77  
 Fever therapy in brucellosis, *March*, 360  
 Febrin foam and film *Sept* 1087  
 in neurosurgery *March* 432  
 Fibrositis, etiology environmental factors, *May* 568  
 Filariasis postwar problem of *July*, 903  
 Fluids administration, in chronic diffuse glomerulonephritis, *Sept.*, 1193  
 in diarrheas of infancy, *July* 882  
 Fluorescence test for dermatophytosis, *March* 325  
 Focal fit *Sept.*, 1115 1122  
 Fractures in hyperparathyroidism *March* 394  
 Frei test *May* 677  
 inverted *May*, 678  
 Friedrich's disease, electrocardiogram in *May* 607  
 Fröblich's syndrome *Sept.*, 1222  
 Functional tests, electrocardiogram in *May* 615  
 Fungus infections, pleural effusions of, *March* 508 511  
 sodium propionate in *March* 438  
 Furmethide in bladder atony *March* 421  
 Furunculosis penicillin in *July* 836  
 GALACTOSE tolerance test of liver function *July* 977  
 Gallbladder disease electrocardiograms in, *May* 606  
 Gastric analysis diagnostic value *March* 492

- Gastritis, diagnosis, *March*, 489  
gastroscopy in, *March*, 498  
Gastroduodenal disease, diagnosis, *March*, 489  
Gastrointestinal tract, acute nonsurgical emergencies related to, *July*, 878  
therapeutics, *March*, 426  
Gastrosocopy, *March*, 497  
Gelatin as blood substitute, *March*, 433, *Sept*, 1091  
Globin insulin in diabetes, *March*, 436  
Globulin, serum, immune, *Sept*, 1087  
Glomerulonephritis, acute, in children, electrocardiogram in, *May*, 606  
penicillin in, *May*, 582  
chronic diffuse, management, *Sept*, 1184  
differential diagnosis, *July*, 990  
Glomerulosclerosis, intercapillary, *March*, 538  
Glucosides, cardiac, *March*, 423, 529  
Glutamic acid in epilepsy, *March*, 418, *Sept*, 1122  
Glycine in myasthenia gravis, *Jan*, 135  
Gold salts therapy in arthritis, *Sept*, 1278  
Gonadotropin therapy in menstrual disorders, *Jan*, 256  
Gonda sign in pyramidal tract lesions, *Jan*, 57  
Gonorrhea, penicillin-resistant, *May*, 688  
sulfonamides in, *Sept*, 1311  
Gordon's sign in pyramidal tract lesions, *Jan*, 53  
Gout, etiology, environmental factors, *May*, 567  
Grafts nerve, *Jan*, 27  
Gramicidin in dermatology, *Sept*, 1107  
Grand mal, *Sept*, 1116, 1122  
Groin, dermatophytosis of, *March*, 323  
Guanidine in myasthenia gravis, *Jan*, 134  
Guillain-Barré syndrome, *Jan*, 1  
HEAD INJURIES in children, coma due to, *July*, 893  
emergency treatment, *July*, 891  
Headache, tension, *May*, 568  
Heart disease, asthma with, in children, *July*, 871  
electrocardiograms in, *May*, 595  
pain of, differential diagnosis, *March*, 513  
quinidine in, *Jan*, 215  
effect of cigarette smoking on, *July*, 949  
emergencies, *Sept*, 1154  
in pediatric practice, *July*, 871  
failure, acute, in children, *July*, 872  
left-sided, *Sept*, 1159  
congestive, with hypertension, *March*, 542  
digitalis in, *March*, 524  
irregularities, electrocardiograms in, *May*, 590  
Heart lesions in hyperparathyroidism, *March*, 395  
position, electrocardiogram and, *May*, 608  
structural abnormalities, electrocardiograms in, *May*, 595  
tamponade, *Sept*, 1158  
therapeutics, *March*, 423  
Heat therapy in rehabilitation, *May*, 787  
Hematoma, subdural, *Jan*, 62  
chronic, diagnosis, importance of, *July*, 1042  
Hemolytic anemia, acute acquired, *May*, 695  
Hemophilia, plasma in, *Sept*, 1085  
Hemoptysis, *July*, 837  
Hemorrhage in liver damage, control of, *March*, 432  
intracranial, convulsions of, *July*, 888  
of early pregnancy, *July*, 853  
of late pregnancy, *July*, 855  
postpartum, *July*, 855, 858  
pulmonary, idiopathic, *July*, 843  
Hemothorax, *March*, 506, 510  
Henoch's purpura, *July*, 880  
Heparin in thrombosis and embolism, *March*, 431, *July*, 933  
Herniation of intervertebral disk, *Jan*, 111  
Hexestrol, *March*, 435  
Hippuric acid test of liver function, *July*, 977  
Histamine-azoprotein in bronchial asthma, *March*, 460  
in migraine, *March*, 438  
Histoplasmosis, *March*, 337  
Hoffman sign in pyramidal tract lesions, *Jan*, 54  
Hormone assays, *Jan*, 254  
Hospitalization, intramural, need for, *May*, 812  
Hospitals, civilian, rehabilitation problem in, *May*, 808  
rehabilitation possibilities in, postwar, *May*, 725  
Hostile-aggressive reactions in returned soldiers, *May*, 735  
Hunner's ulcer, *Sept*, 1205  
Hydatidiform mole, *July*, 854, 856  
Hydrochloric acid in pernicious anemia, *Jan*, 243  
Hydrophobia, immunization, *Sept*, 1243  
Hydrothorax, *March*, 506, 510  
Hyoscine in prevention of motion sickness, *March*, 418  
Hyperimmune serum, *Sept*, 1085  
Hyperinsulinism, *July*, 1014  
Hyperparathyroidism, *March*, 389  
primary, diagnosis, *July*, 1019  
Hyperpyrexia See *Fever therapy*  
Hypertension, arterial, kidneys and, clinical relationships, *March*, 535  
drug therapy, *March*, 425

- Hyperthyroidism *July*, 1013  
 thiouracil in *March* 302, 433  
 Hypnotics in dermatology *Sept.*, 1105  
 in insomnia, *Jan.*, 187  
 Hypocalcemia, electrocardiograms in *May* 613  
 Hypoglycemia, obesity with *Sept.*, 1223  
 Hypomenorrhea, hormone therapy *Jan.*, 260  
 Hypoparathyroidism, treatment, *March* 434 435  
 Hypoproteinemia *Sept.*, 1083  
 human serum albumin in *Sept.*, 1086  
 Hypotension, neosynephrin hydrochloride in, *March*, 420  
 Hypothyroidism obesity with *Sept.*, 1223  
 Immune serum globulin *Sept.*, 1087  
 in brucellosis *March* 359  
 Immunization active, against some common communicable diseases, *Sept.*, 1238  
 combined *Sept.*, 1250  
 Impetigo contagiosa penicillin in *July* 236  
 Industry, fatigue and exhaustion states in, *May* 771  
 Influenzal meningitis serum therapy *Sept.*, 1263, 1266  
 Inguinal buboes, *May* 668  
 Injections, discomfort of means of minimizing *Sept.*, 1238  
 in dermatology *Sept.*, 1104  
 Injuries, head, in children coma due to *July* 893  
 emergency treatment, *July*, 891  
 peripheral nerve *Jan.*, 9  
 Insanity and the criminal *Jan.*, 195  
 legal conceptions *Jan.*, 204  
 malingering and *Jan.*, 205  
 Insomnia, *Jan.*, 178  
 causes of *Jan.*, 180  
 clinical effects, *Jan.*, 181  
 general management, *Jan.* 184  
 hypnotics in, *Jan.*, 187  
 psychotherapy *Jan.*, 186  
 shock therapy in psychotic cases, *Jan.*, 192  
 Insulin, globin in diabetes *March* 436  
 shock therapy in psychoses *Sept.*, 1231  
 with insomnia, *Jan.*, 192  
 Internal medicine in general practice symposium on, *May* 563  
 Intervertebral disk, protrusion of *Jan.*, 111  
 Intocastine, *March* 423  
 Intracranial abscess, emergency treatment, *July* 895  
 hemorrhage, convulsions of *July*, 888  
 Intussusception, *July* 880  
 Iodides in asthma in children, *July* 863  
 in sporotrichosis, *March* 330  
 Iodine in hyperthyroidism, thiouracil and *March* 310  
 Iron deficiency in carcinoma of colon, *July* 958  
 JACKSONIAN epilepsy *Sept.*, 1115 1122  
 Jaundice, acholuric, familial type, *July*, 982  
 Jolly's myasthenic reaction, *Jan.*, 129  
 KEPHIRINE hydrochloride *March* 420  
 Kidneys, arterial hypertension and clinical relationship *March* 535  
 functional tests values in health and disease *Sept.*, 1320  
 infections, nontuberculous, treatment *May* 571  
 lesions in hyperparathyroidism *March* 394  
 Klumpke's paralysis in brachial plexus injuries, *Jan.* 19  
 LABORATORY findings in blood and urine in health and disease *Sept.*, 1314  
 Lanatoside C *March* 424  
 Laryngeal diphtheria, *July* 866  
 Laryngotracheobronchitis, *July* 864  
 Laurence Moon Biedl syndrome, *Sept.*, 1222  
 Lead poisoning in children *July* 881  
 sodium citrate in, *March* 437  
 Lederer's anemia *May* 702  
 Leprosy postwar problem of *July* 907  
 Liniments, *Sept.* 1099  
 Lipotropic substances in cirrhosis of liver *March* 428 483 *May* 658  
 Liver biopsy by aspiration, *March*, 365  
 cirrhosis. See *Cirrhosis of liver*  
 damage to, hemorrhage in, control of *March* 432  
 diseases, diet as factor, *March*, 276 427 484  
 dysfunction, constitutional *July*, 982  
 functional tests *July*, 973  
 composite, *March* 363  
 values in health and disease, *Sept.*, 1319  
 therapy in pernicious anemia, *Jan.* 242  
 Lobectomy in tuberculosis, *March* 451  
 Lobotomy, prefrontal, in psychoses, *Sept.* 1232  
 Lockjaw See *Tetanus*  
 Lotions, dermatologic, *Sept.*, 1097  
 Lumbago etiology *May* 568  
 Lumbar puncture in meningitis, *Sept.* 1264  
 Lung abscess, emergency aspects, *July* 841  
 surgical indications and treatment *Sept.*, 1288



- Lung, carcinoma, emergency aspects, *July*, 842  
 primary surgical indications and treatment, *Sept*, 1282  
 cystic disease, emergency aspects, *July*, 845  
 edema of, acute, emergency aspects, *July*, 837  
 resection, in tuberculosis, *March*, 451  
 Lymphocytic choriomeningitis, benign, *Jan*, 36  
 Lymphogranuloma venereum, *May*, 663  
 diagnosis, *May*, 677  
 extragenital, *May*, 675  
 treatment, *May*, 682  
 Lymphorrhoids in lymphogranuloma venereum, *May*, 670, 671
- MAGNESIUM sulfate in paroxysmal tachycardia, *March*, 426  
 Maladjustment, transitory, in soldiers, reconditioning in, *May*, 751  
 Malaria, postwar problem of, *July*, 902  
 reconditioning the patient, *May*, 760  
 Malingering of insanity to escape criminal responsibility, *Jan*, 205  
 Malta fever See *Brucellosis*  
 Mandelic acid in urinary tract infections, *May*, 574, 576  
 Massage in rehabilitation, *May*, 787  
 Mebaral in epilepsy, *Sept*, 1122  
 Mecholyl, effects on electrocardiogram, *May*, 614  
 in bronchial asthma, *March*, 459  
 Median nerve injuries, *Jan*, 11  
 Median-ulnar nerve injuries, *Jan*, 18  
 Medical emergencies, symposium on, *July*, 833  
 Medullary tractotomy for facial pain, *Jan*, 84  
 Meigs' syndrome, pleural effusion in, *March*, 509, 512  
 Meningitis, acute, emergency treatment *July*, 895  
 Bacillus coli, *Sept*, 1268  
 coma of, emergency treatment, *July*, 893  
 diagnosis, *Sept*, 1260  
 influenzal, serum therapy, *Sept*, 1263, 1266  
 lumbar puncture in, *Sept*, 1264  
 lymphocytic, benign, *Jan*, 36  
 meningococcal, serum therapy, *Sept*, 1263  
 sulfonamides in, *Sept*, 1263, 1310  
 pneumococcal, penicillin in, *May*, 585  
 staphylococcal, penicillin in, *Sept*, 1264, 1267  
 streptococcal, penicillin in, *Sept*, 1264, 1267  
 treatment, *Sept*, 1259, 1262  
 tuberculous, *Sept*, 1267  
 Meningeal arthralgia, *Sept*, 1274
- Menopause, *July*, 1015  
 male, *July*, 1015  
 Menorrhagia, hormone therapy, *Jan*, 259, 261, 264, 266  
 Menstruation, disorders of, diagnostic aids, *Jan*, 252  
 endocrine therapy, *Jan*, 251  
 Mental disease, criminal responsibility and, *Jan*, 195  
 retardation, criminal responsibility and, *Jan*, 208  
 Mercupurin as diuretic, *March*, 424  
 Methenamine in urinary tract infections, *May*, 574, 575  
 Methionine in cirrhosis of liver, *March*, 429, 484  
 Metrazol shock therapy in psychoses, *Sept*, 1232  
 Microsporon infections, *March*, 323  
 Migraine, histamine-azoprotein in, *March*, 438  
 Miscarriage See *Abortion*  
 Mole, hydatidiform, *July*, 854, 856  
 Monilia albicans, infections with, *March*, 323, 328  
 Monoacetyl morphine, *March*, 418  
 Monocaine for local anesthesia, *March*, 419  
 Morphine in convalescence, *Sept*, 1212  
 Motion sickness, treatment, *March*, 418  
 Mouth wash in pernicious anemia, *Jan*, 245  
 Musculocutaneous nerve injuries, *Jan*, 23  
 Myasthenia gravis, diagnostic tests, *Jan*, 128, *March*, 422  
 management, *Jan*, 126, 129  
 treatment, advances in, *March*, 421  
 Myasthenic reaction of Jolly, *Jan*, 129  
 Mycology, medical, *March*, 323  
 Myocardial infarction, restriction of activity in coronary occlusion in relation to, *March*, 405  
 Myocarditis, Fiedler's, electrocardiogram in, *May*, 606  
 Myoclonic jerks, *Sept*, 1117, 1123  
 Myxedema, *July*, 1012
- NARCOLEPSY in children, *July*, 894  
 Narcosynthesis in war neurosis, *May*, 737  
 Nasopharynx, hyperplasia, conductive deafness and, *Sept*, 1251  
 Neck, painful, *May*, 568  
 Needle liver biopsy, *March*, 365  
 Neosphenamine in urinary tract infections, *May*, 577  
 Neostigmine in fasciculation, *March*, 422  
 in myasthenia gravis, diagnostic, *March*, 422  
 therapeutic, *March*, 421  
 in poliomyelitis, *March*, 423  
 in rheumatoid arthritis, *March*, 423



- Penicillin in carbuncles, *July*, 836  
   in cavernous sinus thrombosis, *July*, 894  
   in cellulitis, *May*, 584, *July*, 836  
   in dermatology, *Sept*, 1107  
   in erysipelas and erysipeloid, *July*, 836  
   in furunculosis, *July*, 836  
   in glomerulonephritis, *May*, 582  
   in impetigo contagiosa, *July*, 836  
   in lymphogranuloma venereum, *May*, 682  
   in meningitis, *Sept*, 1264  
   in nonhemolytic streptococcus subacute bacterial endocarditis, *Sept*, 1129  
   in pneumococcal meningitis, *May*, 585  
   in pneumonia, *May*, 580, 582  
   in subacute bacterial endocarditis, *May*, 583  
   in urinary tract infections, *May*, 574, 578  
 inhalant, *July*, 916  
   in bronchiectasis, *Sept*, 1287  
   methods of administration and dosage, *July*, 909  
   snuff, *July*, 916  
   versus sulfonamide therapy, *May*, 579  
 Pentothal narcosynthesis in war neuroses, *May*, 737  
 Peptic ulcer, benign and malignant, differentiation, *March*, 495  
   chronic appendicitis simulating, *May*, 629  
   diagnosis, *March*, 489  
   diet in, fundamental importance, in Army hospital, *May*, 706  
   differential diagnosis, *May*, 624  
   gastric catarrh with, *May*, 628  
   gastroscopy in, *March*, 499  
   in asthenic person, *May*, 625  
   in hypersthenic person, *May*, 626  
   recurrent therapeutic control, *Sept*, 1162  
   roentgen diagnosis, *March*, 493  
   sodium alkyl sulfate in, *March*, 426  
   vitamin "U" therapy, *May*, 709  
   with atypical symptoms, *May*, 625  
 Periarteritis nodosa, *Jan*, 139  
 Pericardial effusion in children, *July*, 871  
 Pericarditis, acute, electrocardiograms in, *May*, 603  
   chronic constrictive, electrocardiograms in, *May*, 604, 609  
 Peripheral nerve injuries, diagnosis and surgical treatment, *Jan*, 9  
 Peritoneal syndrome in nephrosis, *July*, 876  
 Peritoneoscopy in liver disorders, *March*, 369  
 Pernicious anemia, *Jan*, 229  
   clinical types, *Jan*, 230  
   liver therapy, *Jan*, 242  
   posterolateral sclerosis in, management, *Jan*, 245  
 Peroneal nerve injuries, *Jan*, 20  
 Personality patterns, *May*, 746  
 Pertussis, immunization, *Sept*, 1242  
 Petit mal, *Sept*, 1116, 1123  
 Pharmacology, recent advances, *March*, 417  
 Phenobarbital in epilepsy, *Sept*, 1120  
 Phenytoin sodium in epilepsy, *Sept*, 1121  
 Pheochromocytoma of adrenal medulla, *July*, 1016  
 Phlebotomy fever, postwar problem of, *July*, 901  
 Phthalylsulfathiazole See *Sulfathiazole*  
 Physical fitness testing of rheumatic fever patients, *May*, 719  
   medicine, in arthritis, *May*, 790  
   in cerebral palsy, *May*, 792, 819  
   in dermatology, *Sept*, 1111  
   in hospital organization, place of, *May*, 816  
   in poliomyelitis, *May*, 791  
   in rehabilitation, *May*, 786  
   in thrombo-angitis obliterans, *May*, 790  
   in tuberculosis, *May*, 792  
   preventive, *May*, 788  
   rehabilitation, in Army Air Forces, *May*, 717  
   training, of rheumatic fever patients, *May*, 768  
 Pituitary, anterior lobe, disturbances, real vs supposed, *July*, 1010  
   posterior lobe, disturbances, real vs supposed, *July*, 1009  
 Placenta, circumvallate, *July*, 855  
   premature separation, *July*, 855, 857  
   previa, *July*, 855, 857  
 Plague, postwar problem of, *July*, 901  
 Plasma, bovine, for human use, *March*, 433  
   in shock, *Sept*, 1082  
   fractionation, products and uses, *Sept*, 1086  
   heterologous, uses, *Sept*, 1091  
   reactions following use, *Sept*, 1088  
   uses and indications, *Sept*, 1079  
 Pleura, malignant tumors, effusions due to, *March*, 509, 512  
 Pleural effusions, diagnosis and treatment, *March*, 502  
   emergency aspects, *July*, 846  
 Pleurisy, emergency aspects, *July*, 846  
 Pneumococcal meningitis, *Sept*, 1267  
 Pneumonecrosis in tuberculosis, *March*, 451  
 Pneumonia, emergency aspects, *July*, 840  
   in children, *July*, 868  
   penicillin in, *May*, 580, 582  
   pneumococcal, sulfamerazine in, *March*, 294  
   postoperative, prevention, breathing exercises for, *May*, 789  
   sulfonamides in, *Sept*, 1310

- Pneumothorax spontaneous emergency aspects, *July*, 844  
 Polson ivy extracts, *Sept.*, 1105  
 Poisons, ingestion, by children management, *July* 884  
 Poliomyelitis, neostigmine in *March* 423  
 physical medicine in, *May* 791  
 Polyuria in hyperparathyroidism, *March* 395  
 Postpartum hemorrhage, *July*, 855 858  
 infections, *July* 859  
 Postural arthralgia, *Sept.*, 1271  
 Potassium chloride in cataplexy *March* 422  
 in myasthenia gravis, *Jan.*, 135  
 salts, effects on electrocardiogram *May* 613  
 Pourodigin, *March*, 423  
 Powders dermatologic *Sept.*, 1097  
 Precordial pain differential diagnosis *March* 513  
 Pre-eclampsia *March* 538 541 *July*, 850  
 Pregnancy, early hemorrhage of *July* 853  
 ectopic, ruptured, *July* 854 856  
 late, hemorrhage of *July* 855  
 macrocytic anemia of *Jan* 247  
 pernicious vomiting of *July* 848  
 toxemia of *July*, 848  
 Prepuce, redundant, *July* 877  
 Procaine hydrochloride for local anesthesia, *March* 419  
 Proctitis in lymphogranuloma venereum *May* 673  
 Progesterone therapy in menstrual disorders *Jan* 263  
 Promin in tuberculosis, *March* 447 448  
*July* 919  
 Promizole in tuberculosis, *July* 921  
 Propadrine in asthma in children, *July* 867  
 In coryza, *March* 420  
 Propionate-propionie acid ointment in dermatophytosis, *March* 326  
 Prostata, carcinoma, estrogen therapy *March* 435  
 Prostigmine in myasthenia gravis, *Jan.*, 131  
 diagnostic test, *Jan.*, 128  
 Protein serum, in liver disease, *July* 979  
 Prothrombin deficiency plasma in *Sept.*, 1085  
 time in dicoumarol therapy *July* 930  
 in liver disease *July* 978  
 Protrusion of intervertebral disk, *Jan* 111  
 Psychiatric disorders in combat crews overseas, *May* 729  
 in returnees, *May* 733  
 Psychiatrist function of in court *Jan* 211  
 Psychiatry practical *Sept.*, 1231  
 Psychological readjustment in rehabilitation program, Army Air Forces, *May* 723  
 Psychomotor seizure, *Sept.*, 1116 1123  
 Psychoneurosis transitory in soldiers, reconditioning in *May* 751  
 Psychoses, convulsive shock therapy *Sept* 1232  
 criminal responsibility in, *Jan* 195  
 electroshock therapy, outpatient, *Jan.*, 165  
 insulin shock therapy, *Sept.*, 1231  
 prefrontal lobotomy in *Sept* 1232  
 psychotherapy in *Sept.*, 1231  
 war barbiturates in *March*, 418  
 with insomnia electroshock and insulin shock therapy *Jan*, 192  
 Psychosomatic aspects of rehabilitation, *May*, 740  
 principles, *May* 742  
 states, in combat crews, *May* 732  
 in returned soldiers, *May* 736  
 Psychotherapy in fatigue and exhaustion states *May* 781  
 in insomnia, *Jan.*, 186  
 in psychoses, *Sept.*, 1231  
 in recurrent peptic ulcer *Sept* 1162  
 in war neuroses, *May*, 737  
 Psychotic like states in combat crews, *May* 732  
 in returned soldiers, *May* 736  
 Puerperal sepsis *July* 859  
 Pulmonary embolism electrocardiograms in *May* 605  
 emergency aspects *July* 839  
 prevention exercises for *May* 789  
 Pulsus alternans, electrocardiogram in *May* 617  
 Purpura, Henoch's, *July* 880  
 Pyelonephritis, acute diffuse, in children, *July* 875  
 atrophic, *March* 541  
 in hyperparathyroidism *March* 394  
 Pyramidal tract signs, pathologic, *Jan.*, 45  
 QUICK prothrombin time test in dicoumarol therapy *July* 930  
 Quinidine effects on electrocardiogram *May* 611  
 In auricular fibrillation, *Jan.*, 217  
 In auricular flutter *Jan.*, 223  
 in paroxysmal tachycardia *Jan.*, 226  
 uses and abuses, *Jan* 215  
 Quinine test for myasthenia gravis, *Jan.*, 129, *March* 422  
 RABIES, immunization *Sept.*, 1243  
 Racephedrine hydrochloride *March* 420  
 Radial nerve injuries *Jan* 10  
 Radiculoneuritis, acute infections, *Jan.*, 1  
 Raynaud's disease diagnosis, *July* 942

- Reconditioning of malaria patient, *May*, 760  
 of transitorily maladjusted soldiers, *May*, 751  
 program, Army, *May*, 788  
 Army Air Forces, *May*, 717  
 Rectum, stricture, in lymphogranuloma venereum, *May*, 673, 674, 683  
 Rehabilitation, Federal, State and industry's interest in, *May*, 817  
 in Army Air Forces, *May*, 715  
 in civilian medical practice, *May*, 807  
 nutrition in, *May*, 794  
 of malaria patient, *May*, 760  
 of rheumatic fever patients, *May*, 765  
 of transitorily maladjusted soldiers, *May*, 751  
 physical medicine in, *May*, 786  
 postwar possibilities, *May*, 725  
 psychosomatic aspects, *May*, 740  
 symposium on, *May*, 714  
 Respiratory data, laboratory, in health and disease, *Sept*, 1322  
 tract, nonsurgical emergencies, in childhood, *July*, 864  
 Retrogasserian neurotomy, classical, for facial pain, *Jan*, 80  
 posterior, for facial pain, *Jan*, 83  
 Returnees, psychiatric disorders in, *May*, 733  
 Rh factor, blood transfusion and, *Sept*, 1076  
 Rheumatic conditions, etiology, environmental factors, *May*, 566  
 Rheumatic fever, convalescence, physical fitness testing and physical training in, *May*, 719  
 in Army Air Forces, convalescent care, *May*, 765  
 penicillin failure in, *May*, 580  
 pleural effusion in, *March*, 508  
 present-day concepts, *July*, 923  
 sodium salicylate in, *March*, 425  
 sulfadiazine in, prophylactic, *March*, 425  
 Rheumatoid arthritis, *Sept*, 1277  
 etiology, environmental factors, *May*, 566  
 neostigmine in, *March*, 423  
 Riboflavin deficiency, diet in, *May*, 803  
 dosages, *Sept*, 1302  
 Ringworm, *March*, 323  
 Roentgen appearance of skeletal changes in hyperparathyroidism, *July*, 1028  
 diagnosis of carcinoma of stomach, *March*, 495  
 of peptic ulcer, *March*, 493  
 of tuberculosis, rapid screening methods, *March*, 544  
 Roentgenoscopy, protection in, *July*, 1036  
 Rossolimo sign in pyramidal tract lesions, *Jan*, 53
- SALYRGAN-THEOPHYLLINE as diuretic, *March*, 424  
 Sandfly fever, postwar problem of, *July*, 901  
 Sandoz, *March*, 424  
 Scalp, dermatophytosis of, *March*, 323  
 Scarlet fever, immunization, *Sept*, 1247  
 Schistosomiasis, postwar problem of, *July*, 907  
 Schizophrenia, *Jan*, 150  
 modern concept of, *Jan*, 147  
 insulin shock therapy, *Sept*, 1231  
 Sciatic nerve injuries, *Jan*, 20  
 Sciatica, *May*, 569  
 Sclerosis, posterolateral, management in pernicious anemia, *Jan*, 245  
 Scurvy, diet in, *May*, 803  
 Sedatives in convalescence, *Sept*, 1213  
 in psychosomatic disorders, abuse of, *May*, 748  
 Sedimentation rate of erythrocytes, clinical significance, *July*, 937  
 Sepsis, puerperal, *July*, 859  
 Serum albumin, human, *Sept*, 1086  
 blood uses and indications, *Sept*, 1079  
 bovine, despecated, *Sept*, 1091  
 convalescent, *Sept*, 1085  
 globulin, immune, *Sept*, 1087  
 hyperimmune, *Sept*, 1085  
 therapy in meningitis, *Sept*, 1263, 1266  
 Sex glands, disturbances, *July*, 1015  
 Shock, human serum albumin in, *Sept*, 1086  
 in burns, sodium lactate in, *March*, 438  
 plasma in, *Sept*, 1082  
 therapy of psychoses, *Jan*, 165, *Sept*, 1231, 1232  
 prevention of fractures, curare for, *March*, 423  
 Shoulder, painful, *May*, 569  
 Sign of the groove in lymphogranuloma venereum, *May*, 668, 669  
 Silicosis, aluminum powder in, *March*, 437  
 Sinus thrombosis, cavernous, emergency treatment, *July*, 894  
 Skin care in convalescence, *Sept*, 1215  
 diseases, common, treatment, *Sept*, 1095  
 test in brucellosis, *March*, 354  
 Sleeplessness, *Jan*, 178  
 clinical effects, *Jan*, 181  
 treatment, *Jan*, 184  
 Smallpox, immunization, *Sept*, 1247  
 Smoking, recurrent peptic ulcer and, *Sept*, 1169  
 Sodium alkyl sulfate in peptic ulcer, *March*, 426  
 citrate in lead poisoning, *March*, 437  
 lactate in burn shock, *March*, 438  
 propionate in fungus infections, *March*, 438



- Thrombo-angitis obliterans, physical medicine in, *May*, 791
- Thrombosis, cerebral, in children, *July*, 894
- coronary, *March*, 405, *Sept*, 1160
- electrocardiogram in, *May*, 598
- pain of, differential diagnosis, *March*, 513
- quinidine in, *Jan*, 227
- restriction of activity in, and extent of myocardial infarction, *March*, 405
- prevention, dicoumarol in, *July*, 929
- heparin in, *July*, 933
- venous, heparin in, *March*, 431
- Thrush, *March*, 323, 328
- Thymectomy for myasthenia gravis, *Jan*, 136
- Thymus, emergencies associated with, *July*, 860
- Thyroid deficiency, arthralgia due to, *Sept*, 1271
- extract, effects on electrocardiogram, *May*, 611
- in familial periodic paralysis, *March*, 422
- gland, disturbances, real versus supposed, *July*, 1012
- Thyrototoxicosis, thiouracil in, *March*, 302, 433
- Tibial nerve injuries, *Jan*, 22
- Tinea, *March*, 323
- Tobacco, recurrent peptic ulcer and, *Sept*, 1169
- Topical applications, dermatologic, *Sept*, 1096
- Torulosis, *March*, 335
- Toxemia of pregnancy *July*, 848
- preeclamptic, *July*, 850
- Tracheotomy, medullary, for facial pain, *Jan*, 84
- Transfusions, blood, in hemolytic anemia, *May*, 703
- in pernicious anemia, *Jan*, 245
- indications, *Sept*, 1075
- new developments, *Sept*, 1076
- reactions, *Sept*, 1088
- Rh factor in, *Sept*, 1076
- Trends, modern, in internal medicine, *May*, 563
- Trichinosis, electrocardiogram in, *May*, 607
- Trichlorethylene in facial pain, *Jan*, 77
- Trichophytin test for dermatophytosis, *March*, 325
- Trichophytosis, *March*, 323
- Tridione in epilepsy, *Sept*, 1122, 1124
- Trigeminal neuralgia, *Jan*, 73
- atypical, *Jan*, 85
- symptomatic, *Jan*, 75
- Trigger zones in trigeminal neuralgia, *Jan*, 74
- Trigonitis, chronic granular, *Sept*, 1207
- Trömner's technic for Hoffmann sign, *Jan*, 54
- Tropical diseases, postwar aspects, *July*, 897
- Trypanosomiasis, postwar problem of, *July*, 906
- Tuamine sulfate, *March*, 420
- Tuberculosis, chemotherapy, *March*, 445, *July*, 918
- diasone in, *March*, 447, 448, *July*, 921
- physical medicine in, *May*, 792
- promin in, *March*, 447, 448, *July*, 919
- promizole in, *July*, 921
- pulmonary, asymptomatic case, management, *March*, 550
- hemoptysis in, *July*, 837
- modern methods of finding, *March*, 544
- penicillin failure in, *May*, 587
- pleural effusions of, *March*, 507, 511
- surgical treatment, *March*, 449
- treatment, recent advances, *March*, 445
- streptomycin in, *July*, 922
- Tuberculous meningitis, *Sept*, 1267
- Tularemia, pleural effusion in, *March*, 508
- Tumors, facial pain due to, *Jan*, 91
- of brain in children, *July*, 892
- Typhoid fever, immunization, *Sept*, 1245
- Typhus fever, louse-borne, postwar problem of, *July*, 900
- ULCER, Hunner's, *Sept*, 1205
- peptic See *Peptic ulcer*
- Ulnar nerve injuries, *Jan*, 15
- Ulnar-median nerve injuries, *Jan*, 18
- Undecylenate-undecylenic acid ointment in dermatophytosis, *March*, 326
- Undulant fever See *Brucellosis*
- Urea, blood, in liver disease, *July*, 980
- Uremia, convulsions of, *July*, 891
- Urethra, caruncle, *July*, 1007
- diverticulum, *July*, 1008
- female, certain conditions of, *July*, 1005
- mucosa, prolapse of, *July*, 1007
- Urethritis, chronic granular, *Sept*, 1207
- in female, *July*, 1006
- Urgin in heart failure, *March*, 529
- Urinary tract infections, chemotherapy, *May*, 574, 575, *Sept*, 1311
- nontuberculous, treatment, *May*, 571
- nonsurgical emergencies in children, *July*, 874
- Urine, constituents, *Sept*, 1321
- laboratory findings, in health and disease, *Sept*, 1314
- Urobilinogen test for liver function, *July*, 978

- Uterine bleeding functional, hormone therapy, *Jan* 259 261 264 266
- VACCINES in brucellosis, *March* 358  
in lymphogranuloma venereum, *May*, 683
- Van den Bergh test, *July*, 975
- Ventricular gradient *March* 464  
tachycardia, paroxysmal, *Sept.*, 1156
- Veritol *March* 420
- Vitamin A deficiency diet, in *May*, 803  
dosages *Sept.*, 1301
- Vitamin B deficiency, diet in *May* 803  
electrocardiograms in *May*, 603  
dosages, *Sept.*, 1302
- Vitamin C in bronchial asthma *March* 460
- Vitamin D massive doses, in prevention of parathyroid tetany *March* 434
- Vitamin E, massive doses, with dicoumarol, *March* 430
- Vitamin therapy in cirrhosis of liver *March* 279  
in pernicious anemia *Jan* 244
- Vitamin "U" in special convalescent ulcer diet, *May* 709
- Vitamins, deficiencies causes, *Sept.*, 1295  
diagnosis, *Sept.*, 1296  
treatment, *Sept.* 1301  
in dermatology *Sept* 1109  
in present day treatment *Sept* 1294
- Vomiting pernicious, of pregnancy, *July*, 848
- WAR neuroses, *May* 729  
theaters, psychiatric disturbances in *May* 729
- Wasserhelle cell *March* 400
- Wet dressings in acute dermatitis, *July* 834  
in skin disease *Sept.*, 1096
- Whooping cough immunization *Sept.*, 1242
- Wrist clonus in pyramidal tract lesions, *Jan.*, 57
- X RAY treatment of conductive deafness due to lymphoid hyperplasia of nasopharynx, *Sept* 1251
- YEAST brewers' dosages *Sept.*, 1303
- Yellow fever postwar problem of *July* 898





# CONTENTS

## SYMPOSIUM ON RECENT ADVANCES IN GYNECOLOGY AND OBSTETRICS

	PAGE
Foreword	1343
By Dr Norris W Vaux	
Gynecologic Examination—Premarital Counsel	1344
By Dr Robert C. McElroy	
s in the Treatment of Vaginitis	1354
A. E. Rakoff	
of the Vulva and the Problem of Sexual Dissatisfaction	1365
J Edward Lynch	
Chonal Menstrual Disorders Investigation and Endocrine Therapy	1375
By Dr Arthur First	
Endocrine Factors Concerned in Abnormal and Subnormal Genital Development	1387
By Dr Charles William Dunn	
Uses and Abuses of Endocrine Therapy	1396
By Dr Jacob Hoffman	
Dysmenorrhea	1410
By Dr Edward H Bishop	
The Menopause	1416
By Dr John B Montgomery	
The Timing of Ovulation by Basal Temperature Graphs	1425
By Dr Pendleton Tompkins	
Toxemias of Pregnancy	1435
By Dr Mario A. Castallo	
The Management of the Pregnant Cardiac Patient	1449
By Dr Charles W Semisch, III	
Pregnancy and Tuberculosis	1454
By Dr David A Cooper	
Recent Advances in the Management of the Syphilitic Pregnant Woman	1463
By Drs. Herman Beerman and Norman R. Ingraham, Jr	

# CONTENTS

	PAGE
Pregnancy in Diabetes By Dr Ross B Wilson	1477
Puerperal Infection, Its Prevention and Treatment By Dr Mahlon C Hinebaugh, Jr	1483
Vaccination during Pregnancy as a Prophylaxis against Puerperal Infections By Dr J Bernard Bernstine	1495
Some Psychiatric Problems in Obstetrics and Gynecology By Dr Joseph C Yaskin	1508
Management of Home Deliveries By Dr Basil J Giletto	1525
Single Dose and Continuous Spinal Anesthesia for Labor and Vaginal Delivery By Drs Mahlon C Hinebaugh, Jr and Warren R Lang	1538
Some Recent Laboratory Procedures of Importance in Obstetrics and Gynecology By Dr A E Rakoff	1546
Index to Volumes 27, 28 and 29 (1943, 1944 and 1945)	1557

# THE MEDICAL CLINICS

of

## NORTH AMERICA

Vol-29

1945

---

PHILADELPHIA NUMBER

---

### SYMPOSIUM ON RECENT ADVANCES IN GYNECOLOGY AND OBSTETRICS

---

#### FOREWORD

THE work presented in this volume comprises clinical investigation and reports by members of the staffs of Philadelphia hospitals, principally the Philadelphia Lying-in Hospital and the Jefferson Medical College Hospital. The object of this Symposium is to fulfill the need of bringing the recent advances in obstetrics and gynecology to the men in the service as well as to those returned to practice, so that they may have an up-to-date report of the developments which have occurred during the war years. Emphasis has been placed upon the newer methods of therapy as compared with the older methods and the establishment of improved practices in the treatment of gynecologic and obstetric complications.

It is to be understood that some of these practices are still in the experimental stage but since clinical trial has shown that they are worthy of continued use and investigation, they deserve mention in this volume.

This compilation cannot be expected to fulfill the requirements of a complete refresher course in this specialty, but it does point out the improvements and changes that have taken place while the obstetrician-gynecologist was serving his country in other capacities.

Some of the articles have been contributed voluntarily by members of the Philadelphia medical profession and the selection of these contributions has been made with the thorough understanding that the authors are in a position to have established the value of the procedures from clinical experience.

It is hoped that these presentations will not only stimulate additional work and reviews of the specialty but that the profession at large will take advantage of the authors' and publisher's efforts and acquaint themselves with every detail contained therein.

It is with distinct satisfaction that I present this Symposium on the recent advances in obstetrics and gynecology

NORRIS W VAUX, M.D

# GYNECOLOGIC EXAMINATION—PREMARITAL COUNSEL

ROBERT C McELROY, M D

AN introduction to gynecic treatises and study must, of necessity, be concerned with examination of the patient. It is assumed that adequate basic training in the fundamental embryology, anatomy, histology and pathology as related to this field has been acquired

Gynecologic examination is as integral a part of the armamentarium of the general practitioner as it is to the specialist. The great differences in the approach of the two types of practitioner lie in the allotment of the facts in the history taking, time and facility for examination, systematic approach and thoroughness. Errors in diagnosis are due to the sins of omission rather than commission.

Preliminary preparation of the patient for examination requires that the bladder be emptied immediately prior to examination. The rectum should be emptied and enemas utilized when necessary. All constrictive clothing and supportive garments should be removed. Confidence and cooperation of the patient will facilitate matters to the utmost. Gentleness and tact combined with reassurance will mentally prepare the patient for an examination that notoriously carries a stigma of pain and embarrassment. The presence of a nurse, assistant or some third disinterested party serves as protection to the physician but offers little benefit to the patient beyond moral support.

## HISTORY

History taking is a necessary preface to any physical examination. Facts common to all medical history of either specialized or general nature must be noted to cover general and systemic etiologic factors of pelvic disease. Certain facts pertinent to the female in respect to her age, color and marital state (past and present) must be noted. An accurate menstrual history covering age of onset, type of flow, whether regular or irregular, interval, duration and quantity of flow (number of napkins), the character, whether accompanied by clots or passage of tissue, color, odor, association of pain, its location, radiation and character, time in relation to flow, the date of the last menstruation, both normal and abnormal, and finally menopausal symptoms, if the latter be present, must be recorded. Childbearing being responsible for or related to complaints, demands that an accurate obstetrical history include the number of labors and abortions, their respective dates, character and the method of termination, the duration of the puerperia

---

\* Instructor, Department of Obstetrics and Gynecology, School of Medicine, University of Pennsylvania, Assistant Obstetrician and Gynecologist, Philadelphia Lying-in, University of Pennsylvania and Philadelphia General Hospitals

and their final results, the size of the infant and its condition at birth, the number of living or dead children with the cause for the deaths recorded. The presence of leukorrhea with notation of its character, color, odor and production of pruritus will aid in tracing the etiology of this subjective finding.

*Menstrual disturbances* may be an indicator of either pelvic or systemic disease such as tuberculosis, severe anemia, blood dyscrasia or endocrine abnormality not necessarily pelvic. The origin of the bleeding must be determined since urinary and rectal origins may be confused with genital sites.

*Pain* as a gynecologic symptom may be in the form of backache, cramps, tenesmus, headache, dyspareunia, urinary or rectal. What is its reference in the pelvis? It should be recalled that contralateral pain is common in pelvic disease and that reference to distant unrelated areas such as the Curtis-Fitzhugh syndrome may deviate the investigation to another field. Right shoulder pain in ectopic pregnancy, ruptured cyst and post-tubal insufflation all have pelvic origins. Ovarian pain and testicular pain are similar in the production of vertigo and nausea. Tubal pain is sharp and stabbing and associated with abnormal tenderness. Uterine pain may be colicky, constant or pressural in manifestation. Vaginal pain may be associated with burning, tingling and itching.

*Leukorrheal discharges* must be investigated as to origin and causative organisms. For this purpose facilities for stained or wet smears should be at hand. An abnormal leukorrhea should always be regarded with suspicion because it may be the first symptom of malignant disease.

The contiguous urinary tract makes any deviation from the normal act of micturition an accompanying symptom of pelvic disease. Urinary disease such as ureteral dysmenorrhea confuses the examiner and urologic training or aid should be sought. Diurnal frequency, nocturia, urgency, burning, pain, hematuria, incontinence, dribbling and retention are the classic subjective phenomena. Objective findings should take note of the color, turbidity and odor of the urine. Urinary disease may be the prime etiologic factor in association with symptoms found in mild gynecic disease. An outstanding example of this is the trigonitis with small cystocele.

Lower intestinal tract phenomena may be caused by gynecologic disease, and vice versa. The bowel habit, whether featured by constipation or diarrhea, may have an important bearing on the patient's symptoms. Mucous diarrhea is almost diagnostic of pelvic abscess, whether tubal or appendiceal in origin.

The previous medical history should include a notation of surgical procedures and their resultant effects on gynecologic complaints with emphasis on the effect on menses or fertility. In regard to the latter the husband's previous medical history or occupation may contribute information that is valuable.

## GYNECOLOGIC EXAMINATION

**Equipment**—The instruments for gynecologic examination are not numerous but they must be specially adapted to suit the needs of the field. The examining table should be one of adjustable length with the facility to elevate the head and shoulders. The supports for the extremities may utilize either heel rests or leg holders. The covering mattress should be firm, smooth yet comfortable. Drawer space at the foot should contain the equipment to be mentioned below.

**Lighting facility** should be either a no-spot lamp, head mirror or light, or a speculum light. The ordinary goose-neck is awkward and burns the patient and the operator while obstructing the view.

The remainder of the equipment includes rubber gloves, lubricant, various types and sizes of specula, tenacula, dressing forceps, steel or glass catheter, suction curette, dilators, sounds, probes, biopsy forceps, cautery or electro coagulation apparatus, pressometer or Rubin apparatus, microscope, needles and syringes, sterilizer, diaphragm rings, solutions, blood counting apparatus and pessaries.

**Position of the Patient**—The gynecology examination necessitates a variance in position of the patient to secure completeness and accuracy. The recumbent, dorsal lithotomy, Sims', knee-chest and Trendelenburg positions all have peculiar usefulness. Abdominal examination is best in the recumbent, bimanual examination by the dorsal lithotomy, Sims' and knee-chest for fistulas or uterine replacement.

**The Examination**—Proper positioning with adequate coverage to prevent undue exposure is the correct approach to examination. *Abdominal examination* precedes pelvic examination. Tumor masses, tympanites, ascites, rigidity and tenderness as well as peristaltic activity are noted. Tumor masses may be smooth or irregular, firm or elastic and do not produce distention of the flanks. Ascites show a fluid wave, shifting dullness and dullness in the flanks. Tympanites causes uniform distention with the characteristic high-pitched note on percussion. The presence of fetal parts and heart sounds makes pregnancy an easier diagnosis. Rigidity of the abdomen or absence of peristalsis indicates some inflammatory lesion and may be secondary to a pelvic lesion or a complication of it. Tumor masses caused by the urinary bladder may be dispelled by the catheter. Coronal tympany is present in ovarian cysts.

On completion of the abdominal examination the *pelvic examination* is next in order. It is carried out with the gloved hand to protect the operator and to respect the aesthetic sense of the patient. One or both hands may be used depending on the ability to completely explore the pelvis. The patient is cautioned that the examination is discomforting but not painful and she may expedite matters by relaxation and deep breathing.

Fundamentally, the exploration can be accomplished thoroughly by means of the internal and external hands to exert counterpressure. The

size, shape, consistency, motility and tenderness of the organs are determined. An accurate knowledge of the normals is essential, and is gained only by wide experience.

The procedure is begun by inspection and palpation of the external genitalia. Congenital abnormalities, hypertrophy, cutaneous lesions, hair distribution, discharge or swelling are noted. Skin lesions that affect other portions of the body may affect this area. Hair distribution may give a clue to endocrine disease. Swellings may be due to inflammation, tumors, varicose veins or hematomas. Bartholin's glands may be palpated in the bases of the labia majora with their orifices in the labia minora. Vaginal penetration is initiated with one finger, the index, and followed by the middle finger. The patient is asked to strain demonstrating relaxation or the presence of urethrocele, cystocele or rectocele. The urinary meatus is inspected for caruncles, mucosal prolapse or cysts. Milking the urethra produces abnormal discharges from Skene's tubules.

Deep vaginal penetration is completed by pressing against the rectum and perineal body, steadying the elbow against the body or hip to allow free motion of the fingers. Care is exercised not to irritate the clitoris or urethra. The vaginal size, shape, consistency, volume, sensitiveness and local heat are noted as well as masses encroaching on it. The latter include Gartner duct cysts, vaginal inclusion cysts, extra-vaginal tumors and inflammatory lesions. Congenital malformations or fistulas when present should be noted.

The cervix projects into the vaginal vault normally at a right angle causing it to point downward and backward. Deviations of this give valuable clues to the position of the uterus. Retroversion forces the cervix towards the symphysis, upward and forward as does pelvic abscesses, cysts or fibromyomas. Lateral deviations indicate that the uterus is either pushed over by a tumor or pulled over by adhesions. Cervical erosions, ectropions, lacerations, cysts, tumors, hypertrophy and elongation as well as the state of the os may be determined. Descensus must be differentiated from elongation with the sound or vulsellum traction. Vaginal hemorrhage may originate from the cervix or uterine cavity and this can be easily observed.

Above the cervix is the uterine body, which is usually in slight anteversion and ante flexion. It is felt by placing the vaginal fingers anterior to the cervix and attempting to cause the abdominal and vaginal fingers to meet over the symphysis pubis. Absence of the body here indicates some retrodisplacement. The cul-de-sac of Douglas is then explored for the smooth, rounded fundal mass and it is differentiated from abscesses, tumors or hematoceles. Absence of the body in either location indicates midposition or lateral deviation. When the fundus is located, the size, shape, consistency, motility and sensitiveness of the uterus is determined. Retrodisplacements are judged as to adherence and replaceability. Lateral deviation is differentiated from tumors and ad-



hesions The uterine mass is differentiated from other pelvic masses by demarcation or sounding

The uterine ligaments are not easily felt, but the round ligaments may be palpated as a cordlike mass arising from the cornua The uterosacral ligaments are felt in the cul-de-sac and are best noted in pelvic endometriosis or spreading carcinoma

Examination of the adnexa requires skill and experience They are motile for great distances in almost any direction and tend to slide away from the exploring hands The normal tube cannot be palpated but enlargements due to ectopic pregnancy, salpingitis, pyosalpinx or hydrosalpinx can be felt. An ectopic gestation is exquisitely tender while the other conditions show variations in shape and a lesser degree of tenderness The ovary can be palpated, but must be trapped between the abdominal or vaginal hands as well as the lateral pelvic wall It must, therefore, be scooped into this site The ovary has a sensitivity similar to that of the testicle and pressure upon it may produce nausea or vertigo. Cysts have the characteristic elastic feel, except the dermoid, which is stony hard and located anterior to the broad ligament They are freely motile usually, while the parovarian cyst is in close approximation to the uterus and is fixed Free motility may cause confusion with a pedunculated fibroid The small cysts are retention in type while the large ones are proliferative

Completeness demands that the bladder and ureters be palpated for masses or tenderness During the palpation of the latter the uterine arteries may be felt in the lateral fornices

It is truly said the gynecologists make no rectal examinations and the surgeon fails to utilize the vagina The rectum affords an additional portal of entry especially in the virgin or to determine the state of the rectovaginal septum in abscess or endometriosis Rectal tenderness is prominent in appendicitis

*Instrumentation* gives further conclusive evidence by exposure of the vagina and cervix with the speculum Uterine replacement may be accomplished by traction on the cervix with the vulsellum The uterine sound shows the direction and depth of the endometrial cavity and if bleeding is encountered is helpful in the Clark test for fundal carcinoma Intracavity tumors may be felt by this method Before sounding the uterus the date of the last menstruation must be known in order not to produce an abortion, frequently the reason a patient consults the physician The fine probe will locate fistulas or sinus tracts The biopsy forceps should be wisely employed to determine the histopathology of suspicious lesions Insensitiveness of the cervix to manipulation except dilatation affords opportunity for the painless application of cauterization and coagulation procedures to erosions and ectropions Marked superficial vascularity, however, contraindicates cauterization because of the possibility of additional uncontrollable bleeding Intrapelvic infection may be activated by such a procedure

Tubal insufflation may be easily accomplished for sterility study. Endometrial biopsy for malignancy or sterility study may be similarly performed. Postcoital ejaculation specimens of semen may be studied for male fertility. The vaginal smear affords valuable evidence in the hands of the expert for the study of malignancy or hormonal control as well as the treatment of vulvovaginitis in the child. The Hinselmann colposcope may be used by the expert for the study of malignant lesions. The Schuller test of painting the cervix with iodine solution outlines the site for biopsy purposes. The microscopic examination of leukorrheal discharges aids in differentiating trichomonas or moniliasis. The catheterized urinalysis affords more accurate diagnosis of urinary findings, and results in urine which is more suitable for either the Friedman or Aschheim-Zondek tests for pregnancy. The former is now more accurately done as a serum prolactin determination on a qualitative basis of the blood. Further diagnostic aids are found in the dark-field examination of ulcerative lesions for primary lues or in culture for Ducrey bacillus in chancroid. Granulomatous lesions are differentiated by the Frei test for lymphogranuloma venereum or the smear for the Donovan bodies of granuloma inguinale.

On a therapeutic basis the vagina is utilized for douching, Elliott therapy or controlled douching, hormonal substitution by suppository or the intravaginal application of cone radiation therapy for malignancy, as well as the colpostat in radium application or as a site for the insertion of radium needles or radon seeds for cases of intractable hemorrhage in carcinoma that will not respond to other methods.

#### PREMARITAL COUNSEL

Premarital laws of various states require that medical examination of the prospective bride and bridegroom be made to rule out syphilitic and gonorrheal infection prior to marriage. These laws, forcing such examination, afford the physician the opportunity to offer these individuals advice in their new venture, which will serve to prepare them for a happy conjugal life and may prevent future marital unhappiness ending in divorce. Such advice may or may not be requested. It is sufficient to state that it is needed in practically all cases but may be received with antagonism unless the cases are individualized.

The time for the consultation cannot be accurately stated. Parents may provide utopia by their intelligent, early instruction to children when the first questions arise. The child should be led into open, frank discussion by stages until complete knowledge is acquired. Physical fitness is a "must" in all things except the vital functions of marriage and parenthood. Until recently there has been complete neglect of this and even now too much misinformation exists. If possible, instruction should begin before love, engagement and the premarital examination in order to allow sufficient time to emphasize and properly digest all

the considerations. The entire field could only be covered thoroughly by successive consultation with the physician, psychiatrist and marriage counselor.

Consultation with the physician is on an intimate and personal relationship which must be handled with the greatest tact and gentleness. A short but pertinent history of previous illness should be combined with the examination, which should be general as well as pelvic. The physician should bring to light certain definite attitudes, entrenched shames, inhibitions, ignorances and erogenous practices in order to disperse these and possibly aid the groom in his approach and ability to stimulate his bride. Anatomic abnormalities should be noted and, if a tight hymen is present, it should be dilated or stretched with or without the aid of anesthesia and with full consent of both bride and groom. This may be accomplished in several ways. Instruction in douching will serve to dilate the orifice and accustom the vagina to a foreign body. The patient may do the dilation by using her finger or thumb at repeated intervals to enlarge the opening. The physician can accomplish it by slow, forceful dilation without anesthesia and tearing of the hymen. If necessary anesthesia is employed. When dilation is done, the woman can be assured that her first coitus will not be painful or unpleasant.

In the case of the woman who has had unpleasant experiences or who masturbates, assurance can be given that these practices have not harmed her. Such erogenous practices may give an index of stimulation points valuable in reaching a climax later on and the knowledge is passed on to the male as advice without revealing its source. Variant positions should be known and described for satisfactory intercourse. She should be instructed to accept and cooperate with her husband's caresses and to guide him where necessary. The marital act is not a duty or chore simply to be tolerated because marriage vows have been spoken. It is indulged in for expression of love and affection and the pleasure derived therefrom. Simultaneous climax can be reached if sufficient practice is had and the proper areas stimulated. Actual insertion of the phallus should not occur until the female climax is near in cases of premature ejaculation. If this is very premature, urologic advice is recommended. Coitus during the menses is not harmful and may be more satisfactory because of the increase in the sex response at that time. A small douche will remove the messy character of the act. A complete knowledge of contraceptive control is fundamental and the method best suited to the couple advised. The diaphragm is most efficient and where this cannot be fitted, the condom is used until the hymen is dilated to permit the use of a diaphragm. In cases of religious scruples the Ogino-Knaus method of rhythm control is advised. Pregnancy should not be delayed too long since it will complete the final union of the family and serve to cement the marriage.

The prospective groom requires advice particularly since most men have had previous sex experience but on a different basis. Before marriage the act was mainly for carnal satisfaction and usually with an experienced partner. Since the male orgasm is always easily reached, he may fail to consider his wife's reaction and failure of response. First of all he, too, must have a short history and physical examination to rule out disease or abnormalities. His ideas, fears, previous acts and erogenous practices should be brought to light and properly discussed. He must be instructed in his rights and duties to his bride as well as her rights and duties in the marital acts. He knows what his responses and stimulation points are and must be cautioned that they vary greatly with those of his wife. Her response is slower and less complete unless he is a clever lover and willing to cooperate with her and practice until the climax is simultaneous. He must be informed of her stimulation points and the necessity of precoital play until she is near the climax. This is accomplished by the proper mental approach combined with physical stimulation, culminating in complete and satisfactory intercourse. The approach should never be one which ever hints of the vulgar or profane but should be associated with expressions of affection and regard. He should protect his wife from intrusion and never indulge in the act when either partner is fatigued or unreceptive.

Both partners are to be informed that lack of orgasm is not lack of affection and as such does not demand rushing into the use of hormone injections or psychoanalysis. As Dickinson so aptly puts it, "we must combine goodness with the gonads and the new harmonies with hormones." The problem is not an insoluble one and with proper investigation and education the solution can be found. In respect to sex practices don't recommend and don't condemn. In regard to premarital practice don't answer affirmatively or negatively but point out the risks. The individuals should not necessarily know of each others experience because some individuals are unable to tolerate such knowledge.

Physical exercise will stimulate the sex urge and response. Since many women lead a sedentary life this activity should be advised. Men, on the other hand, indulge in exercise for the sheer enjoyment of it. Women fail to do so because it causes excess perspiration and contributes to ruffling of the general appearance. Exercise to the point of fatigue will be harmful and care is exercised not to reach this state.

Finally, the question arises as to who shall be educated in these facts. All groups are in need of such instruction. The colleges and universities are attempting to recognize the urgent need for it and are incorporating such courses in the curriculum. However, many times students are not honestly enrolled in the courses to secure knowledge, but because of the lure of the spicy subjects under discussion. It has been my personal observation that the highly intelligent have a much more

difficult time than others in harmonizing their sexual relations because they are afraid to admit ignorance of the subject and will go to the end to solve the problem themselves before seeking advice. They have more consideration for each other and when a problem arises they will make an attempt at a solution. If this fails they will practice continence or indulge only to satisfy their partner. The lower income groups rarely have these difficulties and certainly they infrequently seek advice. With the existing means of recreation they are able to secure sufficient exercise and are not leading a pace that is killing. They do not, as a rule, take into consideration the financial burden of pregnancy and rarely deny themselves because of an inability to provide a college education for the offspring. It is not intended to imply that they have less consideration for each other but that they more frequently enter into the act for sheer expression and pleasure. They have their problems, nevertheless, and premarital advice should always be available to them and should be offered without being rude.

The physician must preserve dignity and abstain from levity during all of the discussion. He must maintain a sympathetic and helpful attitude. He will remember that through education we can teach success in marriage and parenthood by enlisting effort, courage and intelligence, thus preventing the disastrous terminations of so many marriages in the divorce court. He can promote a new outlook on a problem that deserves more careful consideration than has been given it.

#### BIBLIOGRAPHY

- Bisland, L. H. Some Neglected Aspects of Office Gynecology. *Ohio State M J*, 39 1001 (Nov.) 1943.
- Burch, J. C., and Malla, C. A. The Physiologic Approach to Gynecology. *Oklahoma State M A*, 35(5) 189-193 (May) 1942.
- Curtis, et al. Further Studies in Gynecologic Anatomy and Related Clinical Problems. *Surg, Gynec. & Obst.*, 74 708-727 (March) 1942.
- Dickinson, R. L. Premarital Consultation. *J.A.M.A.*, 117 1687-1692 (Nov) 1941.
- Douglas, G. F. Female Urology as Related to Gynecology. *Urol & Cutan R*, Sept., 1940, pp 573-579.
- Dunne, Desire. The More Common Findings on Routine Pelvic Examination. *Proc Life Extension Examiners*, Nov., Dec., 1941.
- Greenhill, J. P. Some Aspects of Office Gynecology. *J Med*, Feb., 1941.
- Greenhill, J. P. Office Gynecology. Chicago, Yearbook Publishers, 1939.
- Hudgins, A. P. The Doctor Advises the Wife. *West Virginia M J*, Feb 1942, pp 72-79.
- Miller, J. R. Office Gynecology—Diagnostic and Therapeutic Procedures Used by the Specialist Which Are also Available to the General Practitioner. *Virginia M Monthly*, Feb., 1942, pp 56-65.
- Mudd, E. B. H. The Premarital Interview. *Cyclopedia of Medicine, Surgery & the Specialties*. Philadelphia, F. A. Davis Co., 1939.
- Nugent, Fred B. Common Errors in Gynecologic Diagnosis. *Pennsylvania State M J*, Nov., 1943.

- Peightal, T. C. Pelvic Infection—Laboratory Aids in Diagnosis and Treatment. New York State J Med., 36 3 173-180
- Pierson R. N. Experiences in Premarital Council in Private Practice. Michigan State M J., Nov., 1941 pp 884-888
- Shaughnessy F. Premarital Examinations in the United States. J.A.M.A., 118(10) 790-798 (March) 1947
- Ward, George G. The Intelligent Gynecologic Examination. Connecticut State M J., 7(2) Feb., 1943

# ADVANCES IN THE TREATMENT OF VAGINITIS

A E RAKOFF, MD \*

PROGRESS in the treatment of vaginal infections and associated disorders of the vagina during the past several years has resulted from a better understanding of the biology and physiology of the vagina in health and disease as well as from the introduction of new chemotherapeutic drugs, antibiotics and hormonal preparations. Also of importance has been the improvement in the technics of applying medications to the vagina particularly with regard to the development of medications which could be effectively distributed over the entire lower genital tract and of the proper physical and chemical character to mix intimately with the vaginal and cervical secretions <sup>1</sup>

## BIOLOGY OF THE NORMAL VAGINA

The effective treatment of infections and discharges of the vagina requires an appreciation of the mechanism by which the normal biologic characteristics of the vagina are maintained <sup>2</sup>

The vaginal mucosa is under the direct influence of the ovarian hormones. The estrogens are the dominant factor in stimulating proliferation of the vaginal epithelium and thus maintaining a vaginal mucosa of normal thickness. The estrogens are also responsible for the deposition of glycogen in high concentration in the vaginal epithelium, progesterone may aid in this process, while androgens inhibit both proliferation and glycogen deposition. By the combined action of enzymes and bacteria the glycogen of the vaginal epithelium is metabolized and broken down to lactic acid. The resulting acidity of the vagina favors the growth of certain acidophilic bacteria, particularly the lactobacilli of Döderlein. These organisms tend to further increase the acidity of the vagina by utilizing glycogen and the carbohydrates resulting from the enzymatic breakdown of glycogen. The resulting pH of the vaginal secretion thus tends to become stabilized at 4.0 to 5.0 in the normal adult during the period of active ovarian function. Since very few other organisms can thrive in so acid an environment, Döderlein's bacilli quite commonly become established in practically pure culture in the normal vaginal tract. By this mechanism the genital tract is protected from exogenous infection.

In phases of diminished ovarian function such as in childhood, in the immediate postpartum period and in the postmenopausal years the diminished elaboration of estrogenic hormones produces a vaginal mucosa that is of diminished thickness, with little or no glycogen content and a less acid or even alkaline secretion ranging from pH 5.0 to 8.0. Under these latter circumstances Döderlein's bacilli tend to disappear from the vaginal secretion. The presence or absence of the lactobacilli is thus largely dependent upon the vaginal acidity. Almost all patients with a vaginal flora of Döderlein's bacilli alone (so called Grade I vaginal flora) have a vaginal pH ranging from 3.9 to 5.0. The majority of patients with a

---

From the Departments of Obstetrics and Gynecology, Jefferson Medical College and Hospital, Philadelphia

\* Assistant Demonstrator in Obstetrics, Instructor in Gynecology, Jefferson Medical College. Director of the Endocrine Laboratories, Jefferson Hospital

Grade II flora (Döderlein's bacilli plus other organisms) have a vaginal pH ranging from 4.6 to 5.5. In the Grade III type (a mixed flora in which there are no Döderlein's bacilli) the pH generally ranges from 5.1 to 6.0 and even higher in the presence of certain infections.

It is thus quite apparent that, in addition to demonstrating the presence or absence of some specific infecting organism, it is of equal importance to study the vaginal secretion for its cytologic content—as an index of estrogenic function, glycogen content, pH and type of bacterial flora in order adequately to evaluate and treat various types of vaginal infections and discharges.

### "NONSPECIFIC INFECTIONS

Low grade nonspecific infections of the vagina are very commonly encountered. They may occur whenever there has been interference with the mechanism for maintaining the normal physiology of the vagina. In *ovarian dysfunctions* associated with estrogen deficiencies, glycogen concentration becomes diminished, the vaginal acidity is reduced and Döderlein's bacilli are replaced by a variety of organisms. The result is an alteration in the character of the vaginal secretion and not infrequently a low grade diffuse vaginitis. The pH of the vaginal secretion can also be altered by the persistent use of *alkaline* or *irritating chemical douches* thus resulting in the displacement of Döderlein's bacilli by less favorable organisms, but once the latter have established themselves and have created an inflammatory reaction of the vaginal mucosa, this abnormal mechanism may continue despite normal ovarian function. *Mechanical trauma* such as may occur from the long continued use of pessaries can also produce an inflammatory reaction. *Cervical infections* also quite commonly produce a nonspecific vaginitis by constantly decreasing the vaginal acidity with copious amounts of alkaline cervical discharge.

The treatment of these nonspecific infections obviously necessitates the correction of the underlying etiologic factor. If there is an associated ovarian deficiency, this should be corrected by appropriate endocrine therapy. If the cervix is infected, cauterization or conization should be employed where necessary. The use of all irritating douches, the application of irritating chemicals and mechanical trauma should be discontinued. Finally, measures to favor the return of the normal vaginal flora should be instituted. This can be most readily accomplished by creating an acid vaginal media. The use of acid vaginal douches several times daily is quite commonly recommended. For this purpose one may employ simple vinegar, 1 tablespoonful to 2 quarts of water, a saturated solution of boric acid, or lactic acid.<sup>2</sup> A suitable prescription is as follows:

	Gm. or Cc.
R. Chlorthymol	
Menthol	13
Methyl salicylate	20
Lactic in sufficient quantity	2.0
	to make 180.0

Mix and label. A teaspoon in 2 quarts of hot water to be used as a vaginal douche morning and evening.



Much more satisfactory than the acid douche is the use of a water-dispersable acid vaginal jelly\* which can be introduced into the vagina once or twice daily and which remains in contact with the vaginal mucosa over a prolonged period of time and thus more effectively creates a suitable acid medium.<sup>4, 5, 6</sup> A very satisfactory preparation\* consists of acetic acid, oxyquinoline sulfate, ricinoleic acid, boric acid and glycerine in a suitable vehicle. This jelly may be introduced at bedtime by the use of a special vaginal applicator containing 5 cc, which is followed in the morning by a simple acid douche. Persistent use of the vaginal jelly for several weeks generally leads to restoration of the normal vaginal flora which tends to persist provided any other underlying factors have been corrected.

#### ATROPHIC VAGINITIS

In the presence of a marked ovarian deficiency the vaginal mucosa may atrophy to a thin tissue-paperlike structure consisting of only a few layers of cells. Because of the susceptibility of this thin tissue to trauma and because of the associated decrease in vaginal acidity, inflammation, ulceration and infection readily result.

This type of condition can be readily corrected by administering estrogenic hormones in sufficient amount to cause proliferation of the vaginal epithelium and by treating the associated nonspecific infection by the methods already prescribed. A much more specific and rapid cure can be effected by applying the estrogenic hormone locally to the vaginal mucosa. This can be accomplished by the use of vaginal suppositories containing natural and synthetic estrogens or even better we have found the use of a water-dispersable acid jelly containing stilbestrol† in concentration of 0.5 mg per cc. Five cubic centimeters of this jelly can be introduced nightly into the vagina by means of a special applicator and followed the next morning with a simple acid douche. By applying the hormone to the vagina locally intense cornification can be rapidly induced without producing excessive systemic effects of hyperestrogenism. After initial cure has been obtained the jelly may be used once or twice weekly as required to maintain a healthy vaginal mucosa.

#### POSTPARTUM VAGINITIS

A nonspecific vaginitis frequently occurs in the postpartum period because of trauma from delivery, the bathing of the vaginal mucosa with the alkaline secretions from the uterus and cervix, and because the vaginal mucosa has become thin and glycogen-poor in this phase of diminished ovarian function. This type of infection responds quickly to an acid vaginal jelly and acid douches. Even more satisfactory is the

\* Aci-Jel supplied by Ortho Pharmaceutical Corp., Linden, New Jersey

† Generously supplied to us for investigational use as "Gynecological Cream" by Ortho Pharmaceutical Corp., Linden, New Jersey

response which can be obtained with local use of an acid jelly containing stilbestrol as described above.

A procedure which we have found very satisfactory in our post-natal clinic is to have patients with excessive discharge or frank vaginitis use an acid jelly and an acid douche from the fourth to the eighth weeks postpartum. At that time any canterization of the cervix which is necessary can be carried out. If vaginitis persists after the cervix has healed, the use of the stilbestrol jelly will generally effect a rapid cure. When used locally in this fashion it generally does not interfere with lactation.

#### HYPERHORMONAL LEUKORRHEA

An excessive amount of normal vaginal secretion is sometimes encountered, particularly in adolescent girls and young unmarried women. This type of discharge is due to excessive stimulation of the lower genital tract by estrogens, resulting either from a state of hyperestrogenism or marked responsiveness of the vagina and cervix to normal estrogen concentrations. This type of discharge quite normally occurs during pregnancy.

The treatment of this type of leukorrhea is very unsatisfactory. Much can be accomplished by assuring the patient that the discharge is of normal character and not due to infection. A simple saline douche twice daily helps to keep the patient more comfortable. In very troublesome cases methyl testosterone, 5 mg daily, can be given by mouth, this often diminishes the estrogen effect and in this dosage rarely gives rise to untoward androgenic symptoms.

#### TRICHOMONAS VAGINITIS

Trichomonas infestation of the vagina remains one of the most troublesome problems in gynecology. Despite the fact that the condition is extremely prevalent, affecting as much as 25 per cent of some population groups,<sup>1</sup> the method of transmission of the disease is not completely known, consequently there is no specific method of prophylaxis. It is probable that the organism is transferred most commonly from one woman to another by contact with vaginal secretion present on toilet articles, toilet seats, bed pans, and similar hygienic mishaps. Transmission through still water pools is also a possibility. Since 5 to 27 per cent<sup>2</sup> of some groups of men are now known to harbor the organisms in the urethra or prostate, usually in very small numbers, transmission through sexual contact undoubtedly sometimes occurs. It is unlikely that infestation of the vagina occurs with trichomonads from the mouth or intestinal tract since the species of trichomonads from these sources differ morphologically and physiologically from *Trichomonas vaginalis*.

Although it is quite easy to obtain symptomatic relief from *Trichomonas vaginitis*, permanent cure of the condition is often extremely

difficult and prolonged. The trichomonads can be readily killed in the laboratory by simple drying or by exposing them to relatively low concentrations of a great many antiseptics or common laboratory reagents.<sup>9</sup> Even in the vagina the organisms are rapidly destroyed on contact with a great many therapeutic agents. Unfortunately, however, occasional organisms can "hide out" in folds of tissue in the vagina or introitus, in the cervical canal, in the cervical glands, in the urethra<sup>10</sup> and Skene's glands, in the bladder and in Bartholin's glands. Within twenty-four to forty-eight hours after local treatment it is not at all uncommon to again find large numbers of the flagellates in the vaginal tract. Unfortunately it is not possible to reach these occasional organisms which are responsible for reinfestation by systemic chemotherapy. Sulfonamides given by mouth in adequate dosage and penicillin given by injection fail to destroy the organisms. It is, therefore, my studied opinion that the technic of treatment in these resistant cases is often far more important than the drug employed.

Symptomatic relief in almost all cases can be readily obtained by douching persistently twice daily with a simple acid douche, but only rarely will this effect a cure. Even the use of medicated douches containing permanganate, iodine, mercurials or other antiseptic is of no additional help in permanently eradicating the flagellates.

The use of acid vaginal jellies likewise affords symptomatic relief and persistent, twice-daily use cures some of the milder cases.

Sulfonamide jellies when used persistently will effect cures in perhaps a somewhat greater percentage of patients but in our experience have not been useful for the more resistant cases. The sulfonamide jellies are helpful particularly as an adjunct in those cases in which there are associated streptococcal infections. The sulfonamides per se are not highly trichomonadocidal.

Medicated suppositories are generally not as effective as the medicated jellies since they do not diffuse as effectively and frequently do not mix well with the vaginal secretions.

For local treatment of the vagina no technic works as well as the introduction of the drug to be used in powder form diluted with a drying base such as kaolin. Many such preparations are available including arsenicals such as aldarson, acetarsone and carbarsone, silver picrate, argyrol, mercurials, sulfanomides and numerous other antiseptics. Although I have a preference for the pentavalent arsenicals, particularly aldarson,<sup>11</sup> I have been able to obtain satisfactory results with a considerable number of the antiseptic powders diluted with kaolin if the method of treatment has been appropriate.

The essentials of obtaining a cure involve thoroughness, frequency and persistence of treatment. The entire vaginal tract should first be cleansed with saline, 5 per cent sodium bicarbonate or suspensions of kaolin to remove all secretion and mucus. Particular care should be given to the cleansing of the cervix and introitus and any folds or

tissue about the urethra. It is also helpful to dry the tissues of the lower genital tract with a stream of warm air. The powder to be used is then insufflated into the vagina by means of an efficient vaginal insufflator of which there are several available such as the Shelanski or Holmes vaginal spray. The material must be thoroughly dispersed over the entire vagina and some of it should also be blown over the tissues of the introitus. The powder is allowed to remain overnight and the following morning a simple cleansing douche is used. It is important that at the onset treatment should be given daily, preferably every day for five or six days. If it is not possible for the patient to be treated by the physician so frequently she may be taught to give the insufflations herself, while lying in the bathtub, taking *due precaution to avoid increasing the intravaginal pressure* by removing the vaginal guard from the insufflator. The treatment can be effectively and safely given by the patient on those days when it is not possible for her to see the physician. After the initial treatments, insufflations can be given every second day, then every three days and then at less frequent intervals depending upon her progress. The physician must of course guard against cumulative or toxic effects of the particular drug used.

Before treatment is started, particularly in patients who have been unsuccessfully treated previously, it is wise to make a careful search for flagellates in the cervix and urethra by obtaining material from these sources on a bacteriologic loop which is immediately suspended in salt solution and examined at once under the microscope. The urine sediment from a centrifuged catheterized urine specimen should also be thoroughly examined for organisms. In married patients with persistent infestation examination of the prostatic and urethral secretions may also be necessary to rule out the husband as a source of reinfection.

In all persistent or recurrent cases it has been our practice to keep the patient under treatment for three months. After the initial series of treatments, insufflations are given twice weekly and are increased to once daily for two or three days just before and just after menstruation, since this is the period when reinfections are most commonly noted. It has also been our custom to have the patients douche daily with an acid douche throughout the entire menstrual flow. In those cases in which reinfection appears to be coming from the urinary tract or from the tissues anterior to the vagina the patients are advised to powder between the labia with the same medicament that is used for insufflation. This is done three or four times daily. In addition, a urinary antiseptic is prescribed. We have found pyridium to be very satisfactory for this purpose, one tablet four times daily.

When the trichomonads have disappeared from the lower genital tract, it is very helpful in obtaining a permanent cure to restore the normal vaginal flora and acidity as rapidly as possible. This is particularly necessary since *Trichomonas vaginitis* is almost always associated with a Grade III flora. For this purpose we employ an acid vaginal

jelly and an acid douche which is used for several months on days when insufflations are not given. Another problem which sometimes complicates the treatment of some severe cases of *Trichomonas vaginitis* is marked sensitivity of the patient to many drugs. This is sometimes a true allergy but more often the sensitivity is due to the extreme inflammation of the parts. Severe burning, irritation and edema may occur in such individuals after treatment. In this event treatment for the next several days should consist of simple saline douches every few hours, and cold compresses to the labia. After the acute inflammation has subsided insufflations with kaolin alone should be started, and then small increasing amounts of drug gradually added at each treatment.

#### VAGINAL MONILIASIS

Infections of the vagina with monilia and related yeastlike fungi have received considerable attention in the past several years. The infection produces a vulvovaginitis which gives rise to severe itching of the parts often with swelling of the labia and dermatitis of the surrounding skin areas. The discharge is not profuse but has a characteristic thick, cheesy consistency. The vaginal mucosa is generally coated with "thrush" patches. The infection is quite common during pregnancy, occurring in as many as 10 per cent in some prenatal clinics, but it is much less frequent in nonpregnant women. It also has a tendency to occur quite commonly among diabetic women. A high carbohydrate content and increased vaginal acidity favor the growth of the yeastlike fungi, thus explaining the increased frequency in pregnancy and among diabetics. In pregnant women infection may be transmitted to the baby at the time of delivery, thus giving rise to "thrush" in the newborn. Infection of the nipples of lactating women is also occasionally observed.

Moniliasis is a persistent infection and difficult to cure particularly in pregnant women.<sup>12</sup> The hyphae of the fungi tend to grow well into the epithelial layers making it difficult to remove the thrush patches by simple cleansing. Moreover, the yeast cells and spores are not easily destroyed by antiseptics.

Treatment consists in the removal of all thrush patches by gently but thoroughly swabbing the vagina with a 5 per cent solution of sodium bicarbonate or a diluted solution of green soap. The entire lower genital tract is then gently dried with cotton balls or a stream of warm air. The entire mucous membrane, introitus and labia are then painted with an antiseptic solution. There is no question but that gentian violet, 1 or 2 per cent aqueous solution, affords the most relief from the itching and in controlling the infection. However, the disagreeable staining and messiness is a great disadvantage. A considerable advance has resulted from the introduction of a vaginal cream which combines a low concentration of gentian violet with quaternary ammonium salts and possesses no staining properties whatsoever. The

detergent effects of the quaternary salts permits the use of lesser concentrations of gentian violet.\* Moreover, we have found that the use of a jelly or cream base alone even without any added medicament is helpful because it mechanically loosens the thrush patches from the vaginal mucosa and washes them from the vagina. Five cubic centimeters of the cream is introduced into the vagina twice daily. This is followed by the use of a mild alkaline douche, an example of which follows

	Gm. or Cc.
R Zinc sulfate	2 0
Menthol	2.0
Camphor	2.0
Sodium biborate	90
Sodium bicarbonate	90

Mix and label A teaspoon in 2 quarts of water as a douche.

If the vulvar skin has become infected with the fungus, persistent treatment of these areas with the gentian violet jelly or other fungicidal ointments may be necessary.

During pregnancy it is at times necessary to treat the patient off and on throughout the entire gestation. We have never seen this result in any harm. Following delivery these patients frequently make a dramatic spontaneous cure due to the rapidly diminishing supply of glycogen in the lower genital tract.

It should be borne in mind that the male can be infected with monilia resulting in rather severe balanitis. The male can also serve as a source for reinfection of the wife.<sup>13</sup>

#### FUSOSPIRILLOSIS (VINCENT'S INFECTION)

Vaginal infection due to Vincent's organisms are usually associated with and favored by uncleanness. Not infrequently they may result from abnormal sexual practices or autoinoculation from the mouth of women suffering with Vincent's infection of the gums. It also quite commonly occurs as a secondary infection superimposed on other ulcerated lesions especially those of a granulomatous character. The vaginal mucosa and introitus present a 'raw beef' appearance and frequently there are deep ulcerations. The discharge is usually profuse, yellow and foul. Similar infections may be produced by other types of spirilla and spirochetes.

In this condition it is essential to recognize and treat any underlying infection and then to institute effective hygienic measures. The fusospirochilosis generally responds rapidly to insufflation with an arsenical

\* This preparation was generously supplied to us for clinical investigation in the form of Genteral Vaginal Cream by Ortho Pharmaceutical Corp., Linden, New Jersey (The active ingredients may be identified as methyl rosaniline (gentian violet), quaternary ammonium compound and glycerine in a suitable vehicle containing a parahydroxybenzoic acid ester as a preservative.)

drying powder such as that described for *Trichomonas vaginitis*, or frequent daily application of neoarsphenamine, 10 per cent in glycerin, or frequent applications of gentian violet. We have found the use of sulfonamide jellies or creams to be highly effective in the treatment of this condition and much more convenient than the previous methods. For this purpose we have used particularly a cream containing three sulfonamides\* each of which becomes effective at different pH levels. Five cubic centimeters of the cream are introduced twice daily into the vagina and removed after eight hours by a simple cleansing douche.

Recent studies indicate that jellies containing penicillin are also effective in the treatment of this condition, as is penicillin given parenterally<sup>14</sup>

#### VULVOVAGINITIS IN CHILDREN

Vulvovaginitis in children is generally classified as "specific" when it is caused by the gonococcus or "nonspecific" when due to other causes. The nonspecific type of vaginitis in children may result from the introduction of foreign bodies into the vagina, local irritation from manipulation or tight clothing, uncleanness or low grade infections with a variety of organisms. Because of the delicate nature of the epithelial lining of the vagina together with its neutral or alkaline secretion, this structure in little girls is especially susceptible to bacterial infection.

In the treatment of *gonococcal vulvovaginitis* the first essential is strict isolation in order to prevent contamination of the other children in the household or institution. Care should be taken to prevent infection of the eyes or spread of the infection to the rectum. The local use of antiseptics and douches which formerly required many months and sometimes years of persistent therapy to effect a cure have now been replaced by treatment with estrogenic hormone, sulfonamides or penicillin. Each of these methods possess certain advantages and disadvantages.

Estrogenic therapy may be given to cooperative children in the form of vaginal suppositories. A suppository containing 0.05 to 0.1 mg of stilbestrol is inserted each night into the vagina. This is continued for three weeks after which smears are taken at weekly intervals until three negative smears have been obtained. If a cure cannot be effected with two courses of estrogenic therapy it is usually better to proceed with either sulfonamides or penicillin in order to avoid inducing premature sexual changes.

In children in whom local treatment is not possible or feasible, stilbestrol may be given orally 0.1 mg daily for two to three weeks. If

\* Triple-Sulfa Cream, generously supplied to us for clinical investigation by Ortho Pharmaceutical Corp., Linden, New Jersey, contains micronized "sulfa" drugs (identified as sulfathiazole, acetylsulfonamide and benzylsulfanilamide) in a suitable base, nonbuffered to permit optimal pH effectiveness for the "sulfa" compounds.

any tendency toward growth of pubic hair or tenderness of the breast is noted this type of treatment should be stopped at once.

A high percentage of successful results can be obtained with estrogenic therapy in children. In refractory or recurrent cases, examination of the cervix with a cystoscope should be made and the rectum should also be examined for infection. If either of these structures is infected, treatment with sulfonamides or penicillin is indicated.

In a number of clinics treatment with sulfonamides is preferred from the onset. In other clinics estrogens are preferred in order to avoid sensitization to the sulfonamides. Sulfathiazole is the most commonly employed preparation for sulfonamide therapy. The generally recommended dosage is 0.5 gram per pound of body weight per day in four divided doses with an equal amount of sodium bicarbonate which is continued for seven to fourteen days, never longer than three weeks.

Good results can also be obtained with sulfadiazine in half the dose for sulfathiazole.

Preliminary results with penicillin administered locally and parenterally indicate that it is highly effective and will probably prove to be a most valuable method of treatment.<sup>15, 16</sup> As yet the best method of administration and dosage requires further investigation.

In the *nonspecific infections* of children the most important factor is the removal of any underlying cause such as foreign bodies as sources of local irritation. The infection itself will generally respond to the use of antiseptics, suppositories or jellies used persistently through a number of weeks. In the more persistent or severe cases, treatment with the estrogens as described for the gonococcal cases will generally effect a rapid cure. Sulfonamide therapy is not generally indicated in the nonspecific infections.

#### BIBLIOGRAPHY

- 1 Rakoff A. E. and Caspar S. L. The Technic of Vaginal Medication. Penn sylvania M. J., 46:582, 1943
- 2 Rakoff A. E., Fco L. G. and Goldstein, L. The Biologic Characteristics of the Normal Vagina. Am. J. Obst. & Gynec., 47:467, 1944
- 3 Karnaky K. J. Normal Physiologic Douches. South M. J., 30:69, 1937
- 4 Bland P. B. and Rakoff A. E. Leukorrhea, Clinical and Therapeutic Aspects. J.A.M.A., 155:1013, 1940
- 5 Chrisman, R. B., Jr., Clinical Results with the Use of a Buffered Acid Jelly pH 4.5 and Other Jellies of Varying pH in Gynecologic Infections Study of 129 Cases. J. Tennessee State M. A., 35:455, 1942
- 6 Allen, E. and Baum H. C., The Treatment of Vaginitis. Am. J. Obst. & Gynec., 45:246, 1943
- 7 Bland, P. B. and Rakoff A. E. The Incidence of Trichomonads in the Vagina, Mouth and Rectum. J.A.M.A., 188:2013, 1937
- 8 Roth, R. B., Trichomonas Urethritis and Prostatitis. Ven. Dis. Inform., 25:163, 1944
- 9 Johnson G. and Trussell R. E., Experimental Basis for the Chemotherapy of Trichomonas Vaginalis Infestations. I. Proc. Soc. Exper. Biol. & Med., 54:245, 1943



- 10 Bland, P B and Rakoff, A E. *Trichomonas* Infestation of the Female Urinary Tract *Urol & Cutan Rev.*, **44** 698, 1940
- 11 Bland, P B and Rakoff, A E. The Investigation of a New Pentavalent Arsenical, Aldarson, in the Treatment of *Trichomonas Vaginitis* *Am J Obst & Gynec.*, **32** 835, 1936
- 12 Hesseltine, H C Experimental & Clinical Therapy of Vulvovaginal Mycoses *Am J Obst & Gynec.*, **34** 439, 1937
- 13 Bland, P B, Rakoff, A E. and Pincus, I J Experimental Vaginal & Cutaneous Moniliasis *Arch Derm & Syph.*, **36** 760, 1937
- 14 Herrell, W E *Penicillin and Other Antibiotic Agents* Philadelphia, W B Saunders Co., 1945, p 247
- 15 Sandes, G M *Vulvovaginitis in Children* *Brit. M J.*, **1** 160, 1944
- 16 Cohn, A, Studdiford, W E. and Grunstein, I *Penicillin Treatment of Sulfonamide Resistant Gonococci Infections in Female Patients, Preliminary Report* *J.A.M.A.*, **124** 1124, 1944



whitish plaques on a red base which may be secondarily infected due to the patient's scratching. At times the secondary infection may be so pronounced that the condition may resemble follicular vulvitis. Diagnosis is made on the characteristic appearance of the lesion, finding sugar in the urine, and positive smears for the fungus. Culture may be necessary to identify the organism in unusual cases.

Treatment is aimed at eliminating the glycosuria plus the local application of 2 to 5 per cent aqueous solution of gentian violet repeated as often as at twenty-four hour intervals. This latter gives prompt and complete relief from the pruritus which is usually the patient's complaint. It is important to remember that the entire vulva and vagina must be treated with the gentian violet solution when it is applied, otherwise the condition will persist.

**Condylomata Acuminata**—These papillomatous lesions of the vulva, often improperly diagnosed "venereal warts," are not venereal in origin but are due to a virus. They may be found in association with venereal disease, and are to be differentiated from condylomata lata which are syphilitic in origin. Lesions may be few or many in number, vary in size from pin-point to several millimeters in diameter and height, and occur in crops on the vulva and in the vagina. They are sometimes seen in pregnancy and, if left alone, frequently disappear after the gestation has terminated, without treatment. When removal is necessary because of bleeding and irritation (they rarely undergo malignant change) excision using the electrocautery is probably to be preferred. Local applications are of no value.

**Pruritus Vulvae**—Itching of the vulva is one of the complaints often encountered in gynecologic practice. Sometimes its cause may be obvious, more frequently investigation will reveal its background, quite commonly no cause can be determined and we are wont to ascribe the complaint to some form of psychoneurosis. In this latter attitude we may be wrong, it is possible that we have not studied the patient sufficiently or observed her for a satisfactory period of time to make the correct diagnosis. The more common causes of itching involve the specialties of medicine, dermatology, urology, proctology, and gynecology. Accordingly the stubborn case should be studied from these angles. Diabetes, jaundice, rectal conditions and parasites, diseases of the urethra and periurethral glands, infections of the genital tract, atrophic and degenerative changes in the vulvar skin due to estrogen deficiency (?), the various dermatologic lesions which cause itching in other parts of the body, local allergy to vulvar pads, talcum powder and the like, and last but not least, poor hygiene—any can be a cause of itching of the vulvar skin. Thus investigation should include urinalysis, smears, examination of any discharge by the hanging-drop method to exclude trichomoniasis, rectal examination, pelvic examination, and a careful examination of the status of the affected skin itself. Moreover, the serologic examination should not be neglected.

Treatment will depend on whether the pruritus has its foundation in systemic or local factors. Medical causes are treated in the usual fashion. Local conditions are treated appropriately. Symptomatic relief is often afforded by removing discharges with cleansing douches (lactic acid solution, U.S.P.—1 teaspoonful to 2 quarts of water), calamine lotion with phenol, and eucupin and benzocaine ointment are helpful, any of the recognized forms of treatment for trichomoniasis (floraquin, ceepryn, silver picrate, and so forth) may be used, gentian violet in 2 to 5 per cent aqueous solution is specific for fungous infections, estrogen cream (stilbestrol 30 mg to the ounce of vanishing or similar cream) or oil for localunction gives prompt relief to some patients with atrophic or degenerative changes of the vulvar skin possibly associated with estrogen deficiency, poor hygiene can be corrected by proper advice and the proper toilet following urination and defecation can be impressed on the patient. The use of x-rays in treating pruritus of undetermined etiology sometimes gives relief. When relief occurs it is usually prompt and follows the first few exposures. Total exposure should not probably exceed one erythema dose, and this should be given in divided dosage at two to three day intervals by a competent radiologist, or at least under his immediate supervision, in order to avoid dermatitis from the x-rays.

**Kraurosis Vulvae**—Kraurosis vulvae and leukoplakia of the vulva are two conditions often intimately associated in the minds of many physicians. The only thing which both conditions actually have in common is that patients having either condition complain equally bitterly of the pruritus which frequently accompanies the conditions.

Kraurosis vulvae is a term of indeterminate meaning in the literature. It is intended to mean a shrinking or shriveling of the vulva. Actually there is a definite atrophy of the vulvar structures—a flattening of the labia majora and a thinning of the skin which may appear colorless, pale or reddened and often exhibits fissures. The patient's only complaint on occasion may be dyspareunia on entrance due to the constriction of the introitus secondary to the atrophy of the tissues. The pruritus causes scratching and as a result secondary infection is sometimes seen. The cause of the condition is unknown but because it is seen during the period of supposed waning ovarian function and in the postmenopausal state, some authorities feel that it may be associated with estrogen deficiency. Various treatments have been suggested but the results are strikingly similar. Fairly prolonged relief may be obtained by the use of estrogen cream or oil. The use of x-rays has also been recommended but the results are strikingly similar. Fairly prolonged relief may be obtained by the use of estrogen cream or oil. The use of x-rays has also been recommended but the results are strikingly similar. Fairly prolonged relief may be obtained by the use of estrogen cream or oil. The use of x-rays has also been recommended but the results are strikingly similar.

present, may cause dermatitis in unskilled or even skilled hands Ultimately, in patients with dyspareunia and pruritus, the treatment of choice is vulvectomy Asymptomatic atrophic changes may be treated with conservatism, as a matter of fact they require no treatment

**Leukoplakic Vulvitis**—Better called *leukoplakia of the vulva* because leukoplakia may be observed on any epithelial surface, leukoplakic vulvitis is a local or diffuse whitish thickening of the skin of the vulva and perianal areas, with or without the formation of fissures The condition often seems to develop in the perineal and perianal areas, spreading forward to include the labia and clitoris and backward to involve the gluteal cleft Pruritus is the chief complaint again, but the condition may be entirely asymptomatic Secondary infection may be present following scratching The cause of this condition is not known

Treatment by hormones (estrogens and androgens) as advocated by some clinicians has not been generally accepted because the late Doctor Taussig, in his monumental work on this condition, showed that over 50 per cent of the patients he treated for carcinoma of the vulva suffered from leukoplakia of the vulva before the carcinoma developed Accordingly, the condition has become recognized as a definite precancerous lesion and the treatment of choice, either in symptomatic or asymptomatic cases, is vulvectomy

#### ULCERATIVE AND HYPERTROPHIC DISEASES OF THE VULVA

Hypertrophic ulcerations of the vulva, some of which are associated with the development of fistulas, require careful study for their diagnosis and differentiation one from another Included under this heading are chancroid, lymphopathia venereum, granuloma inguinale, tuberculosis, syphilis, fusospirochetosis and carcinoma A definite routine of study is necessary when any such lesion of the vulva is encountered

**Chancroid**—Chancroid, a venereal disease seen more often in men, is associated with a lack of cleanliness The local lesion consists of a painful pustule which ulcerates superficially leaving a reddish granular base without surrounding induration and extremely painful to touch The lesions may be multiple due to autoinoculation Inguinal bubo develops early and is often unilateral when present It may slough or rupture spontaneously and drain freely for some time The infection does not become systemic The causative organism is the streptobacillus of Ducrey which can be identified by smear and culture The intradermal injection of killed organisms produces a local reaction (Ducrey test) which is diagnostic

Treatment consists of the use of sulfanilamide both locally and systemically Allantomide or sulfallantoin cream or jelly applied locally favors healing of the ulcerations Buboës when present are preferably treated early, before rupture, by aspiration Penicillin has not yet been used sufficiently to permit an estimate of its value in treatment

**Lymphopathia Venereum**—More commonly known as *lymphogranuloma inguinale*, this is a venereal disease thought to be due to a filtrable virus. It is seen more commonly among the colored race although its prevalence in white women is on the increase. There are two forms—the one associated with the formation of inguinal buboes with or without draining sinuses is more common in men, and the other which predisposes to rectal stricture seems to be more common in women. These two types of lesions are dependent on the peculiarities of the lymphatic structures of the genitalia of the two sexes. The initial lesion may be a small or large ulceration, superficial or deep, occurring on any portion of the vulva or vagina. If it occurs in the anterior portion an infection of the first type above will develop, if in the fourchette, perineum or perianal area or posterior portion of the lower vagina, an infection of the latter type will result. Diagnosis is made by the Frei test—the intradermal injection of the patient with a killed suspension of the virus collected from the bubo or prepared from infected mouse brain or chick embryo. A positive test after forty-eight hours consists of an elevated firm papule surrounded by an area of erythema. The papule may vesiculate or ulcerate in very strongly positive reactions.

Treatment is unsatisfactory. Sulfanilamide has been used with some good effect but most results are poor. It is considered best not to incise the buboes if they develop, but when liquefaction has occurred the contents can be aspirated. If rectal stricture develops, obstruction is often a late eventuality and may require colostomy. Hypertrophy of the vulva may occur from blockage of the lymphatics and may require vulvectomy.

**Granuloma Inguinale**—This disease involves the vulva, groins, perianal region and inner sides of the thighs. It is more common in Negroes, and is seen in both tropical and temperate zones (at one time it was thought to be a tropical disease). The initial lesion is a small papule which ulcerates to form a soft nontender elevated granulating ulcer of red color. The duration of the disease is unknown but it apparently requires several years for development to the proportions described above. Inguinal adenopathy is unusual. There is a general absence of systemic signs and symptoms. Scarring as a late manifestation may cause hypertrophy of the vulva through obstruction of the lymphatic channels. Diagnosis is made by finding the Donovan bodies in smears taken from the granulomatous lesion and in biopsy specimens.

Treatment is not satisfactory, tartar emetic is given intravenously and fuadin intramuscularly over a prolonged period of time. Recently a case was reported with apparent extragenital lesions of arthritis and osteomyelitis in which treatment with tartar emetic and in addition with sulfadiazine was without effect. Occurrence of such findings should negate the impression that systemic signs and symptoms are not present. Reports on the use of penicillin are not available to date.

**Tuberculosis of the Vulva**—Vulvar tuberculosis is due to a local infec-

tion with the tubercle bacillus. Infection may take place through a break in the skin or through the blood or lymph stream. The lesion is usually a chronically ulcerating growth with elevated edges and an irregular grayish-red granular base with some surrounding infiltration. The ulcers may be superficial or deep, even causing fistulous tracts connecting with the bowel, bladder, or the urethra. The diagnosis is made by making smears and taking a biopsy after suspecting the presence of the condition. The microscopic picture is necessary for certain diagnosis, but even here, granulomas of the vulva due to foreign bodies such as talcum powder may give a microscopic picture which can prove confusing even to the experienced observer.

Treatment will vary with the nature and extent of the lesion, if it is purely local, excision is preferable, if it is too extensive for complete excision, then x-ray treatments are preferable to the application of radium locally because of the sloughing effect of the latter. In the presence of general infection local treatment is without effect except as a palliative.

**Syphilis**—In the vulva, syphilis may appear as either the primary, secondary or tertiary lesion. The primary lesion or chancre may be anywhere but is usually on the labia, vestibule or fourchette. It is a small, elevated, firm, nontender ulceration with a grayish base which exudes serum when the slough is removed. It may be single or multiple due to autoinoculation where folds of vulvar skin are in apposition. Diagnosis is made by darkfield examination which may have to be repeated. The secondary lesions may appear as condylomata lata or mucous patches. Darkfield examination is used here for diagnosis but in the event it is negative, biopsy should be made. The serology is usually positive by the time the secondary lesions manifest themselves. The tertiary lesion or gumma is unusual and for diagnosis biopsy of the edge and surrounding tissue is necessary together with serologic examination. Treatment is standard.

**Fusospirochetosis of the Vulva**—Fusospirochetosis or Vincent's infection of the vulva is occasionally seen. Whether this is a primary or secondary infection is not usually clear. The vulvar skin is edematous and macerated with few or many sloughing, acutely tender ulcerations which are associated with a fetid, acetic discharge. Smears from the ulcerations show the fusiform bacillus and the spirillum. The source of the infection is not always clear, but the use of saliva from an infected mouth as a lubricant during coitus has been considered as a possible mechanism.

Treatment is both local and general. Bed rest is desirable because of the systemic reaction which is often present and the severe pain. Sodium perborate or potassium permanganate douches help local hygiene. Arsphenamine or mapharsen locally and intravenously help to bring relief more quickly. Penicillin is reported to be very effective locally in oral infections and should help greatly here.

ROUTINE OF STUDIES TO WHICH PATIENTS WITH HYPERTROPHIC ULCERATIONS OF THE VULVA SHOULD BE SUBJECTED AND THEIR SIGNIFICANCE

	Etiology	Darfield	Smear	Culture	Serology	Biopsy	Skin Test	Therapeutic Test
Chancroid	Streptobacillus Dreyer	Excludes syphilis.	Positive value.	Difficult but of positive value.	Negative.	Excludes carcinoma.	Negative Dreyer test excludes.	Sulfonamides locally and systemically
Lymphopathia venereum.	Filtrable virus.	Excludes syphilis.	No value except to exclude other conditions.	Shows only second ary invaders.	Negative Complement fixation test with chick anti ven is specific.	Positive value, also excludes carcinoma.	Negative Frit test excludes.	Vaccine plus sulfonamides of ? value.
Gonorrhea (acute or chronic).	Intracellular Donovan bodies are characteristic.	Excludes syphilis.	? value. Donovan bodies may be found.	No value, secondary invaders only.	Negative.	Most important also excludes carcinoma.	No value.	Tartrate emetic, sulfonamides are of value.
Tuberculosis.	Tubercle bacillus.	Excludes syphilis.	? value.	? value and difficult cultural isolation.	Negative.	Most important also excludes carcinoma.	Negative value only.	
Syphilis.	Spirochaeta pallida.	Positive value.	Excludes leprosy, chlamydia.	No value.	Positive Wassermann and Kahn.	Positive value, also excludes carcinoma.	? value.	Antispecific.
Fusospirochetosis ( Vincent's )	Fusiform bacillus and spirochetes ( loose coil )	Doubtful value.	Positive value gentian violet stain.	Most valuable.	Negative.	Excludes carcinoma.	Negative Frit and Dreyer of value to exclude.	Antispecific help. Penicillin very effective locally
Carcinoma.	Unknown.	Excludes syphilis.	Washings stained by Papanicolaou's technique may be of value.	No value.	Negative.	Only positive means for diagnosis.	No value.	



**Carcinoma of the Vulva.**—Vulvar carcinoma is the third most frequent form of genital cancer in the female, being preceded only by the uterine and ovarian forms of malignancy. It may be primary or secondary, the former being by far the most common. It is a disease of advanced age since most reported cases have occurred in the seventh decade of life. The more common sites of origin are the labia, clitoris, vestibule and urinary meatus, and rarely Bartholin's gland. Histologically the growth may be epidermoid or adenocarcinoma depending on the site of origin, the former being more usual. The condition begins as a small nodule, asymptomatic at first, which gradually increases in size and eventually ulcerates. This is what usually brings the patient to the doctor. The diagnosis, when suspected, is confirmed by biopsy. Carcinoma of the vulva, except the clitoris, develops slowly.

Most cases occur in the anterior portion of the vulva from which the lymphatic drainage is through the inguinal nodes. When recognized early, carcinoma of the vulva can be cured by radical vulvectomy and excision of the superficial and deep inguinal glands (Bassett's operation) as advocated by Taussig who claims above 50 per cent cures. Secondary carcinoma, although rare, may be seen and represents metastasis from other genital cancers or chorioepithelioma. The treatment is palliative.

#### THE PROBLEM OF SEXUAL DISSATISFACTION

The role played by the physician in the management of the problem of sexual dissatisfaction, and the related problems of dyspareunia and vaginismus, is that of confessor and adviser. Usually the patient is distraught with fears—fear of the permanency of her marriage, fear that she is not a good wife, and so forth and finally consults a physician in desperation. She does not blurt out her story in so many words, usually it is a long-drawn-out recital of vague pelvic complaints for which the physician can find no basis in actual pelvic disease. Then when he explains that he can find no pathologic changes, and solicitously inquires just what did cause her to come to his office, the true story slowly emerges. Haste is dangerous at this point, it must be remembered that from the patient's viewpoint she is making a confession. The story unfolds slowly because often in the patient's mind it is a confession of her sexual inadequacy. Most often we know that this is a complex built up as the result of a thoughtless or unadaptable husband who is more concerned with himself than their mutual well-being. Here the physician is confronted with a problem which he can solve by using a combination of sympathetic understanding and judicious questioning. The patient cannot be hurried—adequate time must be allowed for her to collect her thoughts and express in her own way the background of her troubles. If for any reason the physician is unable to give such a patient sufficient time, he had better refer her

to someone who is willing and able to spend the necessary time with her, since a rebuff at this stage may be sufficient to prevent her from making a second attempt to straighten out her difficulties

In order to arrive at some idea of the cause of the patient's distress, careful questioning concerning the first sexual experiences is necessary. Often here will be found the answer. Trauma on the part of a young husband ignorant of the elements of coitus, haste because he does not realize that in woman passion must smolder before it bursts into flame, a total lack of consideration on his part during the formative period of the intimacy of their marriage, a warped picture of the significance of sexual relations in marriage on the part of the wife—any or all may be the factor(s) which must be sought out and corrected by suggestion by the physician. All of these factors could be eliminated by a short postmarital check-up by the family physician, in case the couple had not the advantage of a premarital consultation with a physician (which probably would have prevented the difficulty from ever having developed)

Once the problem has been stated and some notion of the cause established, the most desirable move next is a frank talk with the husband, apart from his wife. Some questioning will provide the physician with an idea of his sexual knowledge and experiences (and the most experienced are not the best informed when the satisfaction of two persons is to be considered') and suggest what information should be given. Usually it is well to explain briefly by word and picture or diagram the male and female anatomy and physiology to both parties, either alone or together. Then explain to them why sexual relations are necessary—first for the purpose of procreation and secondly for their mutual pleasure and satisfaction. Allow them to ask questions, if they wish, and answer them in a clear, understandable language. One of the most important points to impress on the husband is the difference in response of male and female to stimulation. In the average male suggestion alone is sufficient stimulation while in the female suggestion plus caresses and repeated stimulation, sometimes over a relatively prolonged period of time, are necessary. Impress and reimpres on the husband that self-control is necessary and remind him that because he may be ready, or even anxious, to consummate relations his wife may not have reached the stage where the act will be pleasurable for her. Explain that at this point the success or failure of the purpose of the act is in the balance. The occurrence of repeated failures on the part of the wife, because of the selfishness of her husband, is part of the background in this problem of sexual dissatisfaction. It is only a short step to the conviction in the mind of the wife that she is sexually inadequate. From there on the number of complaints, real or imaginary, are myriad and the seed of discontent on the part of either husband or wife, or both, may have been sown. I am convinced after questioning many hundreds of married women and their husbands,

that selfishness combined with a lack of consideration and frequently a total ignorance of the elements of coitus on the part of the husband is a far more common cause of sexual dissatisfaction than any supposed or imaginary sexual inadequacy on the part of the wife. There are no more grateful patients than those for whom a problem of this type has been solved by the physician.

The essentials of success in the management of these problems are first of all a sympathetic understanding by the physician of the true situation which exists, tactful questioning of both husband and wife after each has told his or her story to the physician, a careful explanation of the purposes of sexual relations, a brief explanation of the male and female anatomy to both parties, and finally a note of caution to the husband that the old proverb "haste makes waste" applies even to such things as sexual relations.

# FUNCTIONAL MENSTRUAL DISORDERS INVESTIGATION AND ENDOCRINE THERAPY

ARTHUR FIRST, M.D., F.A.C.S.\*

## MENSTRUATION

A PROPER understanding of menstruation is essential to an intelligent interpretation of the many phases of gynecologic physiology and pathology. The morphological processes concerned in menstruation are found to be closely governed by the fundamental physiological activities of (1) the anterior pituitary gland, (2) the ovaries, (3) the uterus and (4) the nervous system.

**Phases**—Generally a complete menstrual cycle averages about twenty-eight days and is divided into four phases: (1) The postmenstrual or period of recuperation, duration four to five days, (2) the pre-ovulatory, proliferative or estrogen phase, average duration fourteen days, (3) the premenstrual, postovulatory, secretory or progesterin phase, duration five days, (4) the menstrual period of dismantling, duration four days.

**The Postmenstrual Phase**—The postmenstrual characteristics of the uterine mucosa are well recognized. Reparative changes occur before the cessation of bleeding and this corresponds to a stage of reconstruction or involution. The rents in continuity of the surface epithelium are repaired by regeneration from the glandular tissue. The glands gradually resume their normal character as the endometrium returns to the proliferative type. The mucosa is thin and contains widely separated, narrow straight glands. In the ovary during this stage, ripening of a primordial follicle into a graafian follicle begins from the stimulating action of the anterior pituitary gland. The estrogenic hormone thus elaborated by the ovary induces growth and vascularity of the endometrium in direct ratio to the quantity produced.

**The Estrogen Phase**—At the beginning the glands are widely separated. On transverse section the space between these structures is about four times the diameter of the gland. Later in this phase they become rather closely packed, moderately tortuous, tubular in outline and extend into the basal layer. They are lined by low columnar epithelium. The nuclei of the cells are centrally placed and stain deeply. There is moderate atrophy in the lumen of the glands. In the ovary about twelve to fifteen days after the beginning of menstruation the graafian follicle is at its maximum size. The follicle is surrounded by a single layer of cells, the membrana granulosa. The fluid within the follicle is discharged into the peritoneal cavity. Large amounts of estrogenic hormone are transported by the blood stream to the uterus to promote growth and vascularity of the endometrium. Immediately following rupture of the follicle the earliest stage of the new corpus luteum is formed. The corpus luteum is a temporary endocrine gland which secretes progesterin. The corpus luteum is at its maximum size about the middle of the second week of the menstrual cycle. It then gradually regresses and finally disappears. The corpus luteum is a temporary endocrine gland which secretes progesterin. The corpus luteum is at its maximum size about the middle of the second week of the menstrual cycle. It then gradually regresses and finally disappears.

proliferation and differentiation of the granulosa cells and ingrowth of the theca lutein cells

*The Progesterin Phase*—In a dual capacity the corpus luteum continues the elaboration of estrogenic principle and also produces another hormone, termed progesterin. This transforms the estrogen primed endometrium into a premenstrual state suitable, should an ovum become fertilized, for nidation.

In this phase the mucosa becomes differentiated into three distinctive layers (1) a compact surface layer, (2) an intervening spongy layer, and (3) immediately overlying the myometrium a basal layer. Marked secretory activity of the surface cells, but more particularly those of the glands, is evident. The epithelium lining the glands is composed of large cells with basal nuclei.

The stroma also shows specific changes. A thin layer of lightly stained large polygonal stroma cells with large round nuclei forms the compact layer of the mucosa. These cells, however, are not equally developed in all areas. They are not unlike the decidual cells of early gestation and are termed pseudodecidual cells. In the middle or spongy layer are found characteristic markedly tortuous glands, closely packed, but separated from each other by strips of stroma cells. The gland lumen is filled with secretion. The basal layer is unchanged. The histology of the progesterin endometrium is similar to that of a two weeks' gestation and only the absence of chorionic villi distinguishes it.

The true premenstrual stage is the period from the cessation of actual production of progesterin to the onset of bleeding and is only about forty-eight hours in duration. The coiled endometrial arteries constrict at the base with a peripheral ischemia and the stroma of the endometrium becomes dehydrated. Subepithelial hematomas appear coalescing into lacunae which begin to bleed into the lumen.

*Types*—There are, according to the modern concept of menstruation, two different types of a menstruating mucosa.

1 *Normal*—In this type, the functional layers (compacta and spongiosa) are dismantled, leaving a raw wound, the base of which is formed by the altered basilar layer. This is the most common type.

2 *Pseudomenstruation*—In this form, menstruation occurs from an inactive or almost resting mucosa. There is no evidence of the premenstrual phase in the mucosa, uterine bleeding occurring from an estrogenic endometrium. This periodic bleeding is not a genuine menstruation, because it is not associated with the characteristic preparatory endometrial changes nor with extensive endometrial desquamation. This inadequate preparation of the endometrium makes proper implantation of the fertilized ovum impossible and explains many cases of sterility in regularly menstruating women.

Other possible causes of pseudomenstruation besides failure of ovulation are imbalance of the two ovarian hormones, estrogen and progesterin, and a uterus which fails to respond to normal ovarian stimulation.

In studying cases of menstrual disorders, a diagnostic premenstrual uterine curettage is important in that it shows the end result of the effect of both estrogen and progesterone activity on the endometrium. If the endometrium is normally responsive the type of ovarian dysfunction can be determined. Day-to-day vaginal smears also determine estrogenic effect and cyclic ovarian changes. The probable date of

ovulation can often be elicited as well as the effectiveness of therapy. The interpretation of the smear consists in finding cells from the basal vaginal layer indicative of estrogen deficiency or cornification of cells from the superficial vaginal layer showing estrogen activity.

**Etiology.**—As the result of anterior pituitary stimulation of the ovaries, estrogen is gradually concentrated in the endometrium. The premenstrual saturation of the follicular hormone in the uterine mucosa finally causes regressive endometrial changes with resultant bleeding.

The role of the corpus luteum hormone is a passive one of maintaining the endometrium intact. Progesterin is capable of nullifying the terminal effects of estrogen described above. When the corpus luteum regresses in the absence of pregnancy, the saturation effects of estrogen on the endometrium are uninhibited and bleeding results. This involution of the corpus luteum is probably brought about as increasing quantities of estrogenic hormone produced by the ovary gradually inhibit the pituitary gland which, therefore, withdraws its stimulation of the corpus luteum about two days before actual bleeding with resultant menstruation.

In addition, an undetermined "bleeding factor" present in the endometrium of the adult woman only appears to be essential for the onset of menstruation. Thus a child will rarely menstruate even though large quantities of both ovarian hormones are administered. Furthermore, women are occasionally encountered who do not menstruate, although they have a normal amount of estrogen in the blood and urine and an active secretory endometrium, indicating, perhaps, an absence of this so-called bleeding factor.

### AMENORRHEA

The term amenorrhea refers to a marked diminution or complete absence of the menstrual flow. It is classified as primary or secondary. The former refers to a total failure of menstruation to appear, and the latter to a cessation of the cycle after its establishment.

Oligomenorrhea is applied to menstruation occurring at intervals of two or three months. Hypomenorrhea refers to regular though scanty menstruation.

Physiological amenorrhea denotes the absence of menstruation during some physiologic process. Pathological amenorrhea refers to the absence of the period as a result of some anatomical disorder.

**Etiology.**—**PHYSIOLOGICAL AMENORRHEA**—Menstruation is nearly always absent during pregnancy and lactation. It is absent before the establishment of puberty, and after the menopause.

**PATHOLOGICAL AMENORRHEA**—The causes of pathological amenorrhea are both general and local.

**General Causes**—1 **Constitutional Diseases.**—The most common constitutional disorder associated with an absence of the menstrual flow is

advanced pulmonary tuberculosis The primary anemias are generally associated with the condition, as may be diabetes, chronic nephritis, and tuberculous infections other than those involving the lungs It may result from profound nervous shock, and it occurs in the advanced stages of organic nervous disease In Manila it was recently reported that in many patients the menses stopped abruptly after the first bombing or soon after internment and before a food deficiency could have any effect.

2 Acute Infectious Diseases—Amenorrhea is often present during convalescence from the acute exanthemas, typhoid fever, malaria and influenza

3 Climatic Influence—Exposure to wet and cold, with sudden chilling of the body or a simple change of environment may result in a temporary check of the menstrual process

*Local Causes*—1 Primary—The most common local cause of amenorrhea is congenital ill-development of the organs fundamentally concerned in menstruation Usually the uterus and ovaries are involved, the hypoplastic alteration in the uterus being secondary to that in the ovaries Hypoplasia of the latter organs may not be congenital, but may represent some pathologic alteration which had its inception in early adolescence Irregular development of the genital organs, especially an imperforate hymen or stenosis of the vagina or cervix, results in a failure of the menstrual flow to appear

2 Secondary—Radical curettage or prolonged radium treatment may cause amenorrhea by destroying the endometrium

Follicle cysts of the ovary as a cause of amenorrhea are not infrequent These may result from the inability of the ovum to penetrate an inflamed, thickened tunica albuginea, or more commonly, may be due to an insufficient hormonal stimulation from the anterior pituitary gland, so that the follicle fails to rupture If the follicle does not rupture, it becomes either atretic or distended with fluid and forms one or more retention cysts Occasionally these cysts elaborate a sufficient quantity of estrogenic hormone to produce prolonged menstrual bleeding

*Endocrinopathic Causes*—Disorders of the endocrine system may be associated with amenorrhea and this is especially true of the anterior pituitary gland and ovaries These disturbances may be classified as 1 Primary Pituitary Deficiency—Primary deficiency of the anterior pituitary lobe is by far the most common form of endocrine disturbance encountered Generally speaking, this condition, if not sufficiently severe to suppress totally ovarian function, is usually one of a mild Frohlich's syndrome (adiposogenital dystrophy) Clinically, these patients are rather short in stature and show distinct stigmas of underactivity of the hypophysis, manifested first by a characteristic mammary mons girdle obesity due to associated involvement of the hypothalamus, secondly by hypertrichosis with masculine distribution

of pubic hair, and thirdly by genital hypoplasia with menstrual derangement.

2 **Primary Ovarian Failure (Primary Hypogonadism)**—Primary ovarian failure is due to inherent deficiency of the internal secretory portion of the ovary independent of the secondary effects of the diminution of function of other glands, notably the pituitary and thyroid. Clinically, these patients present a marked contrast to those of the hypopituitary type. They represent the superlatively feminine type. They are emotional to excess, underweight, visceroptotic and intolerant to food. They experience gastrointestinal spasticity, irritability of the nervous system and dysmenorrhea.

Hypoplasia of the genital organs and irregular menstruation, or amenorrhea, are constant observations. Hormone studies reveal a uniformly low estrogenic level in the blood premenstrually. The most significant finding, however, is a demonstrable quantity of anterior pituitary gonadotropic hormone in the blood and urine in about 50 per cent of the patients.

3 **Thyroid Derangement.**—It is well known that the ovary depends on thyroid secretion to increase its chemical reactions. However amenorrhea occurs more frequently with hyperfunction. Hypothyroidism is more often associated with an excessive flow.

4 **Uterine Factor.**—Amenorrhea sometimes is noted in patients with a normal level of blood and urine estrogen. In these women the uterus becomes atrophic and fails to respond to normal or increased ovarian function. Occasionally, however, one is surprised in obtaining on curettage a normal secretory endometrium. In these patients the absence of the so-called bleeding factor is, perhaps, responsible for the amenorrhea.

Many of the disturbances associated with amenorrhea of endocrine origin are due to worry and anxiety over the nonappearance of the menses rather than to any direct effect of the amenorrhea itself. Most symptoms are relieved when the patient is reassured that amenorrhea does not mean the "retention" of harmful products.

**Treatment.**—The treatment involves the employment of measures to correct the cause. We shall confine ourselves chiefly to a discussion of the endocrine therapy.

**QUANTITATIVE HORMONAL ASSAYS AS GUIDE TO TREATMENT.**—Quantitative hormonal assays of anterior pituitary and ovarian excretion in the urine gives us the best means of "determining endocrine function and therapy in both amenorrhea and dysfunctional uterine bleeding. The following hormonal assays are available for this purpose:

1 **Gonadotropic Hormones.**—Elaborated by the anterior pituitary gland they stimulate the ovaries by means of two specific hormones: the follicle-stimulating and luteinizing hormone. In addition chorionic gonadotropin, somewhat resembling the above is produced by the chorionic cells of the placenta. A twenty-four hour urine specimen is collected and the proteins precipitated by alcohol. Bio-assay is made by injection into infantile mice. These assays are of



value in determining pituitary dysfunction in menstrual disorders and whether we are dealing with primary pituitary failure or primary hypogonadism

2 *Estrogenic Hormones*—For determination of estrogen in the urine, the urine is first hydrolyzed by boiling for fifteen minutes with 5 per cent hydrochloric acid or sulfuric acid. This releases about 95 per cent of the estrogenic hormone present by converting the inactive to active estrogen. During active sex life, except during pregnancy when there is a huge increase, a woman normally excretes in the urine 150 mouse units of estrogen in twenty-four hours.

There is a rise in estrogen at the time of ovulation followed by a drop and then another rise premenstrually. The highest concentration is noted at the end of the premenstrual stage. A modification of the Allen-Doisy test is usually employed in which the extract is injected into castrated adult mice or rats and varying degrees of vaginal estrus observed.

These are accurate and practical tests to determine the level of ovarian activity. They are of special value in the diagnosis of functional sterility in regularly menstruating women. At the premenstrual phase of the cycle, close to 90 per cent of normal fertile women show a demonstrable quantity of the hormone. In regularly menstruating sterile women, without pelvic disease, a positive reaction is much less frequent, thus indicating a deficiency of estrogenic production.

3 *Progesterone and Its Excretion Product, Pregnandiol*—Progesterone is metabolized in the liver and excreted in the urine as a water-soluble compound, sodium pregnandiol glycuronate. Pregnandiol has no biologic action but can be determined in the urine by the gravimetric method of Venning and Browne. In menstrual disorders, the presence of pregnandiol in the urine immediately after ovulation in amounts of 3 to 10 mg is indicative of a normal corpus luteum and ovulation.

4 *Androgens and 17-Ketosteroids*—A woman normally excretes about three fourths as much androgen as the male. This is derived from the adrenal cortex. Biologic assay is difficult. Chemical assay for 17-ketosteroids is employed instead. The term "17-ketosteroids" refers to those steroids possessing a ketone group on the 17th carbon atom. The principle 17-ketosteroids that occur in the normal human urine are androgenic. Therefore they serve in the female as an index of adrenal function.

In female hypogonadism, the 17-ketosteroids may be normal in primary ovarian failure but diminished if due to pituitary deficiency.

In considering endocrine therapy, functional amenorrhea and menorrhagia can practically be discussed together since both represent varying degrees of the same endocrine disturbance. To the woman suffering psychically from amenorrhea of functional origin, it makes no difference whether she is bleeding from a proliferative or a progesterational endometrium. The mental relief is the same. To the woman, however, in whom amenorrhea and sterility coexist, the cure of the latter depends in great measure upon a physiological cure of the underlying uterine ovarian deficiency. We will therefore consider in order the specific therapeutic value of (1) the gonadotropic hormones, (2) the estrogens, (3) progesterone, (4) androgens (testosterone), (5) thyroid.

1 *Gonadotropic Hormones*—The gonadotropic hormones available are as follows:

(a) *Hypophyseal Gonadotropin*—Extracted from fresh anterior

pituitary glands of sheep and horse, it contains both follicle-stimulating and luteinizing fractions. Its value lies, therefore, in its ability to stimulate a hypofunctioning ovary if due to a pituitary gonadotropic deficiency. It does not cause ovulation. Injections should be stopped after three weeks of the cycle and after three months of cyclical administration due to the danger of producing follicle cysts of the ovary. It is employed in amenorrhea and in functional uterine bleeding due to deficient luteinization. The commercial preparations available contain 25 to 500 rat units per cubic centimeter.

(b) **Equine Gonadotropin**.—Extracted from the serum of pregnant mares, it is mostly a follicle-stimulating hormone and only slightly a luteinizing hormone. In amenorrhea associated with genital hypoplasia, it is administered in doses of 200 to 400 I U intramuscularly three times a week for two weeks followed by a two weeks' rest or a course of chorionic gonadotropin.

(c) **Chorionic Gonadotropins**.—Extracted from the urine and placenta of pregnant women, its biologic effect is chiefly a luteinizing one. It has no value in the treatment of amenorrhea unless preceded by hypophyseal gonadotropin in the first two weeks to cause follicle maturation. Then it may be given as 500 I U daily for two weeks.

In uterine bleeding due to progesterone deficiency 500 I U are recommended three times weekly.

(d) **Combined Hypophyseal and Chorionic Gonadotropin**.—This product is indicated in any disorder due to failure of ovulation. One cubic centimeter is given intramuscularly three times a week. Not more than 5 to 10 cc. should be given a month due to the danger of producing hemorrhagic and cystic ovaries.

2 **Estrogens**.—The estrogenic hormones are both natural and synthetic. Standardization is in terms of international unit defined as the estrogenic activity of 0.001 mg. of estrone, as rat unit—1 R.U. being equivalent to 5–10 I.U., and by weight, in milligrams of active substance. It is administered intramuscularly, orally, locally and in decho-lin may be given intravenously.

For amenorrhea 50,000 I U are given three times weekly for two weeks, followed by a course of progesterone and repeated monthly.

The chief value of estrogens is to stimulate uterine growth in patients with primary ovarian deficiency. At best it is only substitution therapy. Its advocacy in functional bleeding is questionable except where an atrophic endometrium is present. Ovulation may be inhibited and bleeding stopped for a while but withdrawal bleeding may be severe especially in a patient with a hyperplastic endometrium.

Danger of prolonged usage inhibiting the pituitary and ovary should be emphasized.

3 **Progesterone**.—This may be administered intramuscularly or orally as pregnenolone, 1 mg. being equivalent to 0.2 mg. of progesterone by injection.

Secondary amenorrhéas respond after the administration of 20 mg of progesterone given daily for three days (Zondek). It is better, however, especially if the amenorrhéa is of longer duration than six months to prime the endometrium first with large doses of estrogen. Zondek recommends 1 mg of alpha-estradiol given together with 10 mg of progesterone daily for five days.

Progesterone may be of value in functional uterine bleeding if due to a progesterone deficiency such as is found in cases of hyperplasia of the endometrium. Ten mg are injected twice weekly for the last two weeks of the cycle.

4 *Androgens*—Testosterone may be given intramuscularly, sublingually, as a pellet under the skin or orally as methyl testosterone which is one-fifth as effective as the intramuscular injection. The danger of producing hirsutism should be kept in mind and may probably be avoided by limiting the dosage to 300 mg per month and discontinuing it as soon as acne is evident. It is of great value in inhibiting some of the effects of estrogen on the endometrium and myometrium and in inhibiting the gonadotropic function of the pituitary. It tends to produce an atrophic endometrium. It is of special value, therefore, in functional uterine bleeding, 25 mg are injected three times weekly.

5 *Thyroid*—This is a valuable adjuvant in the treatment of functional amenorrhéa and bleeding and may be used even when the basal metabolism is normal, or slightly subnormal. The administration of desiccated thyroid tissue, 0.09 or 0.13 gm ( $1\frac{1}{2}$  or 2 grains) daily, tends to increase cellular activity throughout the entire body, including the endocrine glands. In addition, it has been shown that thyroid extract neutralizes the action of estrogenic substance on the endometrium. This may explain the temporary beneficial effect of thyroid therapy in functional uterine bleeding when prolonged and unantagonized activity of estrogenic substance on the endometrium is the immediate cause of the abnormal uterine hemorrhage.

*Prostigmine* has been used in the treatment of delayed menstruation. One mg is injected on three consecutive days. Estrogenic substances release acetylcholine in the uterus which produces local hyperemia. Prostigmine is a nonspecific agent with a similar property of potentiating the action of acetylcholine. If no menstrual flow occurs within seventy-two hours after the last injection a tentative diagnosis of pregnancy is made.

*Insulin*—This drug may restore normal menstruation in some patients, especially those who are underweight and suffering with primary ovarian underactivity.

*Irradiation Therapy*—Low dosage irradiation of the pituitary gland and ovaries is a valuable measure in the treatment of functional amenorrhéa as well as menorrhagia of endocrine origin. The therapeutic action of irradiation is generally attributed to a transitory or permanent increase in cellular activity of the ovary. X-ray stimulation of the ovaries

is contraindicated in the absence of a subthreshold quantity of blood estrogen, as it may induce permanent amenorrhea.

Ovarian irradiation is only partially effective when the ovarian hypofunction is secondary to hypophyseal or thyroid underactivity. In such instances irradiation of the pituitary appears to have an adjuvant value. Low dosage irradiation of the pituitary gland and ovaries affords the best results in the treatment of menstrual disturbances with functional sterility associated. Strict adherence to the technic of the roentgenologist is most essential, i.e., from 50 to 80 roentgen units or about 10 per cent skin erythema dose being given once a week over a period of six weeks. The one menstrual disorder that almost invariably fails to respond is hypomenorrhea (scanty flow) in regularly menstruating women. The cause of the menstrual deficiency in these patients is apparently within the uterus itself.

### MENORRHAGIA

This term is applied to excessive menstruation, or to an undue prolongation of the flow. It may be anatomical or functional, the latter diagnosis being arrived at by exclusion.

**Etiology—ANATOMIC TYPES**—The anatomical causes of menorrhagia are either general or local. These may be considered under the following:

**General Causes**—1 **Blood Disease**.—In patients with a hemorrhagic tendency menorrhagia is commonly present. It may be the first symptom of purpura hemorrhagica, leukemia, aplastic anemia, and Hodgkin's disease.

2 **Systemic Disease**.—Disease of the cardiovascular apparatus, kidney or liver disease, resulting in a tardy return circulation, favors engorgement of the pelvic vessels. This naturally leads to uterine congestion and excessive menstruation. In addition, disorders of the arterial system associated with high tension or endarteritis may be a factor.

3 **Hypothyroidism**.—The menorrhagia often noted in myxedema and minor degrees of thyroid hypofunction illustrates the degree to which the ovary is dependent upon normal thyroid function.

**Local Causes**—1 **Inflammation**.—Inflammation, either acute, subacute or chronic, of the cervix, uterine body, fallopian tubes, ovaries, pelvic peritoneum, or pelvic cellular tissue, is nearly always associated with excessive menstrual discharge.

2 **Ulcerations**.—Ulcerations of the cervix or vagina, whether simple, tuberculous, syphilitic or malignant, provoke excessive menstrual discharge. In this category may be listed senile vaginitis, ill-fitting pessary and prolapse of the uterus.

3 **Neoplasms**.—Tumors, both benign and malignant, involving the cervix, endometrium, myometrium, or serous covering of the uterus may cause profuse and prolonged menstruation. Myomas of the inter-

stitial type may be influential, but not to the same extent as those of the submucous variety. Subserous tumors, if small, do not cause bleeding, but if of large size, owing to pressure engorgement, abnormal hemorrhage may occur.

**DYSFUNCTIONAL UTERINE BLEEDING**—Bleeding of endocrine origin is termed functional bleeding. This term is a misnomer. More aptly it should be called dysfunctional uterine bleeding. An interval shorter than sixteen days or a flow lasting more than eight days is abnormal. The endocrine organs most commonly responsible for excessive menstruation are the pituitary gland and ovaries. Thyroid dysfunction may, likewise, provoke free menstrual bleeding.

Functional menorrhagia is especially common (1) with the onset of puberty and (2) in the early menopause, although it not infrequently occurs in mature women under 40 years of age.

Functional menstrual disorders result from an ovarian failure. This may be primary due to inherent ovarian disease or secondary to extra-ovarian causes such as pituitary disease or other endocrine lesions or various types of constitutional disease. The approximate degree of ovarian involvement is indicated by the endometrium.

In patients with this symptom, uterine curettage usually reveals a hyperplastic endometrium characterized by a dense vascular stromal and epithelial overgrowth. The glands are large and cystic, representing the characteristic "Swiss cheese" pattern, large dilated glands being found side by side with others small and narrow. Many of these are lined by several layers of epithelial cells and show no secretion in the lumen.

Functional bleeding is usually due to deficient activity of the anterior pituitary lobe. This deficiency results in an imbalance of the two hormones of the ovary manifested by a prolonged production of the estrogenic hormone. This is associated with an absence or deficiency of the corpus luteum hormone. The abnormal development of the unantagonized follicle due to the failure of luteinization results in follicular cysts of varying size.

In the early menopause a certain number of women exhibit a tendency to menorrhagia or metrorrhagia. After eliminating carcinoma, myoma or polyps as causative factors by performing a diagnostic curettage, a functional origin must be considered. In these patients sclerotic changes in the ovarian parenchyma and the tunica albuginea render the follicle incapable of completing its cycle or of responding to a normal or even an increased pituitary function.

Occasionally, postmenopausal uterine bleeding is encountered, due probably to a temporary reactivation of the graafian follicle. This condition must be distinguished from granulosa cell tumors of the ovary which produce similar clinical and endometrial changes.

**Treatment of Functional Uterine Bleeding**—In the treatment of bleeding of endocrine origin the mere removal of the hyperplastic endome-

trium does not bring about permanent cure. Unless the underlying endocrine disorder is overcome, the condition will recur

The treatment of functional uterine hemorrhage may be considered under three groups (1) pubescent bleeding, (2) maturity bleeding and (3) menopausal bleeding

1 *Pubescent Bleeding*—In pubertal bleeding the ovary is usually at fault, i.e., there is an absence of progesterin, except in the rare instances of Fröhlich's disease. One generally finds a high gonadotropin and low estrogen curve. The endometrium may be hyperplastic or atrophic. The treatment recommended for the more serious cases is as follows

- (a) The vagina should be packed through a Kelly cystoscope.
- (b) A blood transfusion.
- (c) Desiccated thyroid,  $\frac{1}{2}$  grain three times daily
- (d) Insulin hypodermatically 5 to 10 units, before the morning and evening meal, improves health and has a definite ovarian influence.
- (e) Progesterone, 10 mg injected twice weekly. Occasionally this may precipitate bleeding
- (f) Testosterone. This affords, as a rule, better results than other endocrine therapy. In the first week 150 mg may be required followed by 50 mg per week for several months, gradually reducing the dosage.
- (g) Low dosage irradiation of the ovaries (50 to 80 roentgen units per treatment) may be used as an adjunct in certain cases.

2 *Maturity Bleeding*—During the childbearing period the administration of gonadotropic anterior pituitary-like hormone acts, it is claimed, as a specific. This hormone has a tendency to complete luteinization and is, therefore, a logical form of treatment for women under 40. One thousand rat units are given hypodermically daily until the bleeding subsides and every other day for two months thereafter. In obstinate cases, low dosage irradiation of the pituitary gland and ovaries has proved of value. Snake venom has been recommended and favorable results have been reported following the administration of this material.

Biskind presents evidence that menorrhagia and premenstrual tension related to an excess of estrogen, are caused by failure of the liver to inactivate estrogen because of deficiency of the vitamin B complex. Administration of B complex orally in daily doses of thiamine 9 mg., riboflavin 9 mg., nicotinamide 75 mg., led to prompt improvement of these conditions

3 *Menopausal Bleeding*—Patients approaching the menopause often show a compensatory excess of the gonadotropic hormone of the anterior hypophysis. The administration of gonadotropic hormone is, therefore, of no value. The injection of 300 mg of testosterone propionate over a period of one month, it is claimed, is of value. Radium is the treatment of choice.

*Radium in Functional Bleeding*—If abnormal menstrual bleeding fails to respond to the simple measure outlined, radium may be used

but this should be employed only after ordinary means have failed. In the early menstrual life of women, only small doses of radium should be administered, and then, too, with extreme caution on account of the probability of inducing sterility or establishing a premature menopause. Temporary and even permanent amenorrhea may follow a 200 or 300 mg.-hr. dose. After the menopause, however, 600 to 1500 milligram-hours may be administered with impunity.

# ENDOCRINE FACTORS CONCERNED IN ABNORMAL AND SUBNORMAL GENITAL DEVELOPMENT

CHARLES WILLIAM DUNN, M.D., F.A.C.P.\*

THE postnatal development of the female genital tract, its accessory organs and the female secondary characteristics are directly controlled by hormonal factors contained in the anterior-pituitary-gonadal axis. The anterior pituitary gonadotropic factor activates the ovary to development and at the same time increases its hormonal function during the prepuberty years. This is a gradual and progressive process during the first decade of life and while not biologically demonstrable in early childhood it is physically and psychologically evident. Not until the tenth year of life is definite evidence present that the anterior pituitary-gonadal mechanism exists. The first objective evidence that this axis is operating is obtained by the demonstration of the anterior pituitary gonadotropic factor in the urine. A few months after this event an increase in the titer of estrogen is found. A few years later as puberty is approached the anterior pituitary-gonadal axis begins to exhibit its normal cyclic phases of excretion, characterized by a rise in anterior pituitary excretion to a peak point and a more gradual rise in estrogen secretion. These cycles continue until the estrogen excretion reaches a peak of premenstrual titer while at the same time the anterior pituitary gonadotropic secretion has fallen to its low cyclic point. These cycles are regularly maintained until the menarche occurs and thereafter normally maintain themselves during the reproductive period of life. At some variable period of time, probably a few years after the menarche, the reproductive human female structure the ova becomes part of this lunar cycle. This, briefly, represents the primary normal functional role of the anterior pituitary-gonadal axis and its hormonal sphere of activity.

The majority of young females possess a normally functioning anterior pituitary-gonadal axis and therefore one observes during childhood a progression of developmental events, which are constituted as feminine physique and psyche, feminine attributes, internal and external feminine genital organs and feminine secondary sex characteristics. However, the pattern of sex is genetically laid down during fertilization of the ova and is established during early embryonic development and fetal maturation.

Anomalies of development occur in the female genital tract which are construed as being primarily of genetic origin, with possibly early

Assistant Professor of Medicine Graduate School of Medicine  
of Pennsylvania, Philadelphia.



hormonic influences as a supplemental cause. It must be remembered that basically the body develops from two corresponding embryonic segments and that the primary and secondary genital organs and structures develop from the mullerian and wolffian ducts which in turn have a common segmental embryonic origin. It is the influence of the primary genetic factor and the hormonal dominance activating the embryonic structures which determine the sexual normal or abnormal pattern. It is when there is some alteration from normal influences that we observe developmental anomalies, the most typical of which is hermaphroditism or pseudohermaphroditism.

#### HERMAPHRODITISM AND PSEUDOHERMAPHRODITISM

True hermaphroditism is rare and is characterized by an internal and external genital tract which is made up one-half of masculine structures and the other half of feminine structures. Externally the genital area shows a moderately developed penis and a testis and a rudimentary vagina. A pseudo-hypospadias exists in most instances, and also present are well-developed breasts. The hirsute pattern may be heterosexual. The physical features are predominately feminine, however, the female appearing to respond psychologically to the dominance of the genital pattern. In such cases one cannot be guided exclusively by the hormonal assay in arriving at the final disposition of the case. It is a far safer procedure to request exploratory laparotomy, investigate the pelvic structures and be guided by the dominance of the internal anatomical development, provided the parent in the case of minors is fully apprised of the ultimate physiologic importance of Nature's own biologic reactions. In adults the problem is more complex because certain of these individuals have economically established themselves in one sex or the other. For example, a structurally developed adult female pseudohermaphrodite had established herself in a male occupation. She sacrificed her genital internal organs and proceeded in life as a male.

Such unfortunate states should be corrected as was done in the case of T.S., early in life, and who until age four years, was raised as a female. During hospitalization for a tonsillectomy and adenoidectomy, anomalies of the genital external tract were observed. These were an enlarged clitoris, abnormally large labia and imperforate vagina. Examination and closer inspection revealed that the labia had rudimentary rugae, the enlarged clitoris was an underdeveloped penis, the normally placed urethral opening for the female was actually a hypospadias, the imperforate vagina was actually a cleft type, anomalous scrotal development and careful palpation showed very small testes high in the inguinal canal.

In this instance we were dealing with a male in spite of the fact that the abnormal external genital structures resembled those of the female. A picture of the opposite type was obtained in the case of B.L., to be described presently, who had a greatly hypertrophied (male size) clitoris.

## HYPERTROPHY OF THE CLITORIS

The human embryo develops from bilateral segments which are similar in structure. The genital organs and urogenital tract develop from the same segmental site and from two structures, the wolffian and müllerian ducts. Under genetic and hormonal influences the müllerian ducts develop into the female genital and gonadal structures and from the wolffian structure develop corresponding male organs. However, in the female, certain wolffian structures, from which the male generative and genital organs develop, do not completely fail to differentiate and possess masculine features. This type of tissue is found principally in the clitoris but may be present also in the ovary in the form of rests or inclusions of medullary cords or tubules and the latter remain as potentially androgenic-producing tissues, whereas the clitoris will react and develop under androgenic stimulation. Thus in the female genital tract we have one structure which is responsive to androgenic stimulation and sometimes in the ovary one structure which can develop into tissue which is capable of producing androgens. The clitoris hypertrophies because it is sensitive to stimulation by the androgens. The abnormal quantities of androgens which stimulate the clitoris to develop to abnormal sizes and often produce an erectile response arise from an arrhenoblastoma or an adrenal rest tumor of the ovary, from a hyperfunctional adrenal cortex or from hermaphroditic organs. The degree of clitoral hypertrophy and its progression depends upon the androgenic activity of the tissue at fault. The hypertrophy of the clitoris represents only a part of the total endocrinous picture. Other features are advancement of general and secondary hair growth, acne, advanced muscular development, deepening of the voice pitch, and a general physical tendency towards masculine attributes.

Fortunately, a hypertrophied clitoris which has developed because of the presence of abnormal quantities of androgens will return to its normal proportions when the androgens are restored to normal levels. The treatment of this hypertrophy is removal of the endocrine element which generates it—the ovarian arrhenoblastoma or adrenal rest or the adrenal cortical tumor, benign or malignant. The presence of the former is best determined by exploratory operation in young female children and of the latter by perirenal air injection. Occasionally, however, all possible measures fail to reveal the source of the androgens and quite properly the surgeon will not sacrifice either gland in the hope that he will remove the cause of the condition.

Patient B.L.'s clitoris was enlarged to the size of the penis of a 16 year old male and erected frequently day and night. Her physical build was strongly masculine, she was staturally overdeveloped, the voice was of deep pitch, hirsuties of the male type were present. Exploratory laparotomy revealed normal appearing ovaries and internal genitals and palpation of the adrenals showed them to be apparently normal. The exploratory laparotomy was completed and resection



Thus we had a three year history of prematurity in hair growth, which began in a nongenital area. I have observed a number of young female children with markedly excessive and generalized body and extremity hair growth. My observations of these individuals together with a large group of adolescent and adult females with hypertrichosis has led me to classify the cases in four etiological groups (1) Cushing syndrome including arrhenoblastoma of the ovary, (2) adrenal cortical hyperplasia or adenoma, (3) the hereditary type and (4) increased sensitivity of the hair follicle end organ to androgenic stimulation. The case of M.N. belongs primarily in the last group but because of the maternal tendency to mild and localized abnormal hair growth an hereditary factor might also be considered as present. The usual progression of events in the case of M.N. would be that in a year or two excessive hair growth will be observed in the lateral facial regions, the outer portions of the upper lip, the submental regions and eventually on the body in general. If good ovarian function develops and estrogens are normal or above normal in quantity the likelihood is that the hypertrichotic tendency will be controlled. If the hereditary factor is prominent or there develops an intercurrent adrenal cortical hyperplasia, possibly due to failure of the adrenal cortex to involute properly from the enlarged state of infancy, the likelihood of good ovarian function diminishes. The ovarian failure is incidental to the deleterious influence of the adrenal cortical hormone on the ovary. Another type of deleterious reaction on the ovary follows mumps. The importance of the latter is not generally recognized.

#### RETARDED DEVELOPMENTAL STATES

The anterior pituitary gonadotropic factor is the motor of the ovary. The primary and secondary female sex organs normally are in an abated state of development during the first decade of life. A minor degree of growth occurs in the primary internal and external genital structure during this period but this growth is chiefly in the structural tissues of these organs and is essentially a somatic growth effect and is not accompanied by an increase in functional capacity. This growth is nevertheless extremely important to the organ's subsequent functional capacity and is also effected by endocrine factors, namely, thyroid hormone and anterior pituitary growth factor operating as general stimulators of somatic and cellular development. If a thyroid deficiency exists during the first decade of body development, when the female sex organs are in an essentially functional dormant state, one is likely to have a deficit in early development and a delay in functional development when the second decade is entered. The anterior pituitary growth factor might be said to exert itself in the development and maturity of the cell mass whereas the thyroid is especially active in giving vitality and integrity to body cell mass. The early postnatal growth of tissues in the genital structures is

part of the general body growth and is produced by the combined influences of the anterior pituitary growth hormone and thyroid hormone. The loss of this synergistic hormonal effect is well demonstrated in the cretin. Thyroid hormone is very essential to the normal development of all cells and particularly those cellular changes which are concerned with the higher functional capacity, the reproductive cells and tissues are definitely in this classification. Thus many functional disorders of the internal genital organs are the result of early or later acquired thyroid or anterior pituitary deficiency and in the adult range from sterility to metrorrhagia. Therefore, in subnormal developments of the genital tract and retarded genital functional development we must investigate for anterior pituitary and thyroid deficiencies as well as a deficiency in the anterior pituitary-gonadal axis. The general features of this type of disorder are compositely represented in pituitary infantilism and often persists to adult life producing a major psychological and sociological problem.

D. H., an unmarried woman 24 years of age, typifies this clinical problem. Since the age of 12 years she had sought treatment for her statural and sexual underdevelopment. She is 57 inches tall, weighs 113 pounds, and the relationship of the lower measurement, span and height are proportionate. The wrist formation is atypically achondroplastic. Mentally she is depressed, chiefly because of the primary amenorrhea, infantile genitalia, very deficient pubic and axillary hair and absence of breast development. The thyroid was small and doughy soft in texture such as is found in the secondary type of hypothyroidism.

In general a therapeutic regimen for this patient appeared to be futile, nevertheless a therapeutic program was instituted to stimulate breast development and general tissue response. The therapy consisted in the administration of estynyl (Schering) 0.05 mg. nightly and the twice daily administration of a capsule containing 1 grain of anterior pituitary,  $\frac{1}{8}$  grain of thyroid, U.S.P., and 2 grains of calcium glycerophosphate. In one month a mass about the size of a half walnut was felt beneath both nipples. The estynyl was reduced to every third night. In two months the breast tissue had developed to the size of half a small lemon, uterine bleeding first appeared at this time and persisted for thirty-six hours. One month later on June 8, 1945, a normal five-day menstrual period occurred and the breasts were the size of half a medium orange. The psychological change in this patient is solely due to her breast development and the appearance of the (therapeutic) menstrual flow.

The role of the adrenal cortex, pineal and thymus glands in genital development is not too clearly defined. We do know that hyperfunctional adrenal cortical states do have a depressant effect upon ovarian development and function. The ovaries in this disorder show diminished size and atretic follicles and because of diminished estrogen production, the breasts and the uterus are small.

#### VIRGINAL GYNECOMASTIA DUE TO INCREASED SENSITIVITY OF END ORGAN TO HORMONIC STIMULATION

Recently another factor has entered the field of discussion of growth development—the factor of the sensitivity of the tissue end organ to

the hormonal stimulator We have shown that the receptiveness of the end organ to hormonal stimulation occurs in an increased, diminished and in normal states The following case illustrates one type of altered end organ response to hormonal stimulation which can occur

S D., a female child, aged  $5\frac{1}{2}$  years, experienced development of the right breast which began one year ago and is now the size of the early pubertal state. The left mammary region is normal for her age. Excessive statural growth is present, her height being 53.5 inches with proportions of trunk, lower measure and span approximating that of a normal 10 year old child Axillary and pubic hair are present, together with an excessive generalized body growth of hair which corresponds in length texture and quality to that present in the axillary and pubic regions. The mental and psychological development is normal



Fig 179.—Virginal gynecomastia in infant (P M) eighteen months of age, onset at age one year

In my opinion this unilateral virginal gynecomastia represents an instance of increased sensitivity of the end organ of the breast parenchyma to estrogenic stimulation. Were excessive amounts of estrogen present one should observe bilateral virginal gynecomastia, epithelial tissue response of the uterine endometrium and the vaginal mucosa, and general advancement of feminization, all of which are absent. The normal responses of the patient are present in her mental and psychological age, the absence of uterine and vaginal response, the normal stage of development of the left mammary area and the general absence of precociousness The abnormalities, exhibited as an increased

sensitivity of the end organ to hormonal stimulation, are unilateral virginal gynecomastia, excessive statural development and incipient hypertrichosis

**Virginal Gynecomastia in a Female Infant Aged 18 Months**—Premature development of the breast may occur as early as one year. It may be present as a unilateral or bilateral abnormality but it occurs more frequently as a bilateral state.

In P. M., a female infant aged 18 months, breast development was first observed at the age of 1 year. The breast tissue developed rapidly in both mammary regions and at times appeared to cause the infant discomfort (Fig. 179). During the past few months no increase in size of the breast has been noted. The birth weight was 8 pounds 2 ounces, the height 26 inches. First dentition occurred at 4½ months and the infant walked at 10½ months. At present the height is 33 inches, lower measurement 14½ inches. Sixteen teeth are present. The breasts are 2½ inches in diameter and 1½ inches deep. The breast parenchyma is 1½ by ¾ inches. The nipple and areola are developed. The breasts appear to be sensitive. The external genitalia are of normal size for age. A vaginal discharge has been observed.

While I believe that in most instances, whether it occurs in the female or the male, gynecomastia is a condition of increased sensitivity of the end organ of the breast cell to estrogenic stimulation and is not amenable to *rational* endocrine therapy which considers the body tissues as a complete functional unit, this disorder should not be dismissed as such until granulosa cell tumors of the ovary are excluded by hormonal assay and complete physical and clinical investigation. Besides producing premature breast development, granulosa cell tumors and luteoma also produce premature feminization and uterine bleeding because such tumors produce excessive and demonstrable amounts of estrogen (estradiol).

#### HYPERTROPHY OF THE BREAST

This condition is similar to virginal gynecomastia and may be unilateral or bilateral and may or may not be associated with signs of painful engorgement preceding the onset of the menarche or premenstruals. For the painful engorgement I am opposed to the use of male hormone in young females. A more practical and harmless treatment is to stimulate urinary excretion and deplete the system of the estrogen by the use of a saline diuretic and fruit juices. A special brassiere or one that uplifts the breasts, particularly on the axillary side, should be worn.

Plastic surgery is the only means of correcting unilateral or bilateral hypertrophy of the breast if the overdevelopment of the breasts is producing physical discomfort or psychologic reactions. However, before this is definitely decided upon it is well to remind the patient that their present size, which she feels she cannot tolerate, may be an asset during later years when breast atrophy normally occurs. This

compensating thought will frequently dampen a patient's desire for plastic surgery

#### APLASIA AND HYPOPLASIA OF THE BREAST

Many young females apparently mature normally—later adult history proves their fertility—and yet their breasts never have developed or are markedly hypoplastic. I believe that the aplasia and hypoplasia present in these cases represent an opposite state to that which is observed in virginal gynecomastia, namely, diminished end organ sensitivity to estrogenic stimulation. I have proved this conception to my own satisfaction by showing after local inunction of estrogenic ointment and oral and hypodermic administration of estrogen have failed to develop the breast, that the injection of 2.5 to 5 mg. of estradiol dipropionate directly into the dense tissue under the nipple will develop it. Not until the estrogen in concentrated strength is brought directly into contact with the breast cells do they respond to stimulation. Unfortunately many such cases require protracted periods of these treatments to obtain reasonably satisfactory results but there are other cases which appear to progress satisfactorily once the breast cells are adequately activated. The oral administration of estinyl appears to be the most active stimulator of the breast tissues when aplasia and hypoplasia of the breast are present.

#### SUMMARY

While the anterior pituitary gonadal axis and its hormones are the chief hormonal factors concerned in feminine genital development, other hormones either act as supplements or independently on the primary and secondary genital structures and the sex characteristics of the female. During the periods of development to puberty the thyroid particularly and possibly the anterior pituitary growth hormone supplement the effects of estrogen on genital structures, and on the development of the feminine physique and psyche.

The treatment of abnormalities of female genital organs depends upon the type of abnormality present. Hormone-producing tumors should be treated surgically. Replacement endocrine therapy is applicable only in deficiency states. Inhibitive therapy, such as the administration of estrogens to combat androgenic excess, can be utilized in a limited group of cases under the circumstances described. Abnormalities in the tissue end organ response to hormonal stimulation require special therapeutic management.



## USES AND ABUSES OF ENDOCRINE THERAPY

JACOB HOFFMAN, M D \*

ENDOCRINOLOGIC research continues to increase our knowledge of gonadal and reproductive physiology and add to the number of diagnostic technics and potent hormonal preparations useful in gynecologic disorders. The physiologic and diagnostic aspects of gynecic endocrinology still remain vague and confusing to many practitioners, but all have found within their grasp the numerous biologically potent sex hormones now available for clinical use. It is easy to understand their eagerness to employ these substances in the treatment of amenorrhea, uterine bleeding, dysmenorrhea, habitual abortion, sterility and other gynecologic disorders which have so long baffled the clinician. Unfortunately, when they turn to the medical literature for guidance in the application of these hormones, they are soon bewildered by the widely divergent views expressed by apparently equally competent investigators. Some maintain that organotherapy deserves a prominent place in the treatment of functional gynecologic disorders, while others insist that its sphere of usefulness is limited and its efficacy questionable.

While many of the more optimistic reports are undoubtedly in good faith, they cannot be accepted at face value either because of their failure to use controls, or to take into account the fact that a large percentage of such disorders, particularly in younger women, are subject to spontaneous correction or respond readily to general hygienic measures and psychic suggestion. The psychotherapeutic effect of organotherapy, especially where the hypodermic route is used, should be borne in mind when evaluating the results of treatment. In following the evolution of organotherapy, one is struck by the fact that brilliant results have been reported at one time or another in virtually all disorders affecting the sexual sphere, with all the sex hormones, given singly or in combination, whether in relatively inert or potent form, and whether given in large or ridiculously small doses. Investigators reporting favorable results have often been led by their subsequent experience to modify or reverse their original judgment. Unfortunately, this may either fail to come to the practitioner's attention or be obscured by persistent allusions to the original favorable reports, contained in the pharmaceutical literature which reaches him at frequent intervals.

Some general practitioners and even some gynecologists, acting in good faith, continue to employ organotherapy after doubt has been cast on its efficacy, because they are loathe to relinquish one therapeutic weapon before another is offered to take its place. Their "give it anyhow" attitude is justifiable only if the treatment is certain to be harmless, and the thought that something concrete is being done is

---

\* Associate in Gynecology, Jefferson Medical College, Pathologist in Gynecology, Jefferson Medical College Hospital, Philadelphia

likely to have a favorable psychological effect on the patient commensurate with the expense incurred. Unfortunately, sex hormone therapy used promiscuously and without a rational basis may often do harm.

For example, the estrogens, though stimulative in their effect on the müllerian derivatives, may have a depressive effect on the anterior pituitary and ovary, defeating the ultimate aim of treatment. Since these substances exert multiple effects in the organism, the clinician who aims at one target may find himself striking others which he had no intention of hitting. Thus, estrogens used for gonorrheal vaginitis in young girls may occasionally cause cystic mastitis.<sup>1</sup> If administered for the control of vasomotor symptoms in post-menopausal women, they may induce uterine bleeding, necessitating curettage and the immediate application of radium until malignancy can be excluded.<sup>2, 3</sup> This has been a fairly common experience since this form of therapy became popular. The carcinogenic action of the estrogens, of which there is suggestive though not conclusive evidence in the human being<sup>4</sup> should be borne in mind, particularly where there is a familial history of genital or mammary cancer.

The use of androgenic substances in the female is obviously nonphysiologic. Aside from their possible masculinizing effect, their suppressive action on the ovary in the susceptible case, may prove more lasting than was originally intended. The gonadotropes now available for clinical use, whether of anterior pituitary equine or chorionic origin, are likely to be of little value and, under some circumstances, may even do harm. In the light of the clinical evidence at hand, it is doubtful whether they can initiate normal cyclic changes, including follicular maturation, ovulation and corpus luteum formation, in the hypofunctioning human ovary. Chorionic gonadotropin from human pregnancy urine may even have a depressive effect.<sup>5</sup> According to Hartman,<sup>6</sup> it acts as a powerful disrupting agent. A combination of anterior pituitary or equine gonadotropin and chorionic gonadotropin, given either simultaneously or in succession, may cause pathologic enlargement of human ovaries with formation of numerous cystic follicles or lutein cysts.<sup>7, 8</sup> While it is claimed that these alterations are transient, we cannot exclude the possibility that the application of forces capable of causing such complete disruption may do lasting damage to the sensitive ovary.

Before resorting to any form of sex hormone therapy, *it is of the utmost importance to eliminate organic disease*. I have often encountered women harboring organic lesions who were previously subjected to prolonged hormone treatment for menopausal bleeding without a preliminary diagnostic curettage and, in some instances, without pelvic examination. Where no organic cause is demonstrable, endocrine therapy should be withheld pending proof that an actual hormonal deficiency exists. The task of establishing a deficiency is not a simple one, even in the hands of the experienced observer with all known diagnostic aids at his disposal. The tests designed for measuring the sex hormone content of the blood and urine provide only limited information, of which the interpretation is not always clear. Hormone titers show wide variations between different individuals and at different times in the same individual. Moreover, variations in technique between one laboratory and another have made it difficult to establish norms or to decide what constitutes a significant deviation.

from normal. The large majority of cases encountered in the gynecologic clinic fail to show deviations sufficiently striking to be significant or conclusive. Where a marked deviation is encountered, its interpretation may present difficulties, due to our incomplete understanding of the factors controlling the level of the sex hormones in the body fluids. The rates of production, utilization, conversion or destruction of the hormones are only a few of the variables which may affect the results.

In my experience and that of others,<sup>9</sup> the most reliable and significant information is provided by histologic examination of endometrial curettings. This procedure will disclose organic lesions of the uterine cavity and in addition may provide a clue to the functional status of the ovary and its governing gland, the anterior pituitary. A thorough physical examination in the nude, with particular attention to the developmental status of the genitalia and secondary sex characters as well as the presence of endocrine stigmata, may also yield valuable information.

The hormones now on the market for the treatment of functional gynecologic disorders include the gonadotropins derived from anterior pituitary gland tissue, human pregnancy urine (chorionic gonadotropin) and serum of pregnant mares (equine gonadotropin), natural and synthetic estrogens, progesterone and pregnenolone, and natural and synthetic androgens. Space permits only a brief discussion of the disorders for which these substances have been recommended, the theories advanced to justify their use, and the possible beneficial and harmful consequences of their use.

#### FUNCTIONAL UTERINE BLEEDING

The sex hormones are widely used for the control or cure of functional uterine bleeding, particularly that associated with endometrial hyperplasia. Progesterone<sup>10</sup> and the orally active progestational substance, pregnenolone,<sup>11</sup> have been advocated on the assumption that they will override the effect of the endogenous estrogens on the uterine mucosa and thus prevent excessive mucosal proliferation and bleeding. Some believe these substances inhibit the myometrial contractions and thus reduce the rate of blood flow to the endometrium. Evaluation of their efficacy in uterine bleeding is difficult because of the frequent tendency to spontaneous coagulation and the possible curative effect of other measures. Further, curettage, often performed on diagnostic purposes but bound not to injure the endometrium, is advocated by some workers. It is also attributed its apparent beneficial effect to its ability to alter the functional capacity of the endometrial blood vessels. In the author's opinion, there would seem to be no rational basis for the use of this hormone in a condition which is

supplied endogenously in adequate or excessive amounts Hartman,<sup>6</sup> in a recent communication, expresses a similar view.

Androgen therapy<sup>14</sup> for the control of excessive uterine bleeding has recently become popular. Its anti-bleeding action has been variously explained on the basis of suppression of estrogen production indirectly by way of the anterior hypophysis, nullification of the effect of endogenous estrogens on the uterine mucosa, inhibition of myometrial contractions with consequent reduction of the blood flow to the endometrium, and conversion to progesterone which in turn prevents excessive mucosal proliferation and bleeding. This form of therapy would appear undesirable and at times hazardous, especially in younger women. Aside from the possible masculinizing effect of the androgens, their depressive action on the ovary and endometrium may interfere with the restoration of normal ovarian and menstrual function.

In view of evidence that persistent follicular activity without ovulation or corpus luteum formation is responsible for abnormal bleeding from a hyperplastic mucosa, many clinicians<sup>15-18</sup> have turned to the gonadotropins with the hope of correcting the underlying ovarian disturbance and thus restoring normal menstrual periodicity. To date, there is no convincing proof that these hormones can favorably affect the ovarian alterations and lead to normal cyclic activity. Hartman's experience with chorionic gonadotropin led him to conclude that there is no physiological basis for its use in bleeding associated with endometrial hyperplasia.<sup>6</sup> He believes that the natural extracts of anterior pituitary gland tissue may eventually offer the best solution for inducing ovulation and corpus luteum formation in cystic and hypotypical human ovaries. Thus he bases on the report of Casida and his associates<sup>17</sup> that crude bovine anterior pituitary extract, given in a single intravenous injection to sterile cows with cystic ovaries and endometrial hyperplasia, induced ovulation as shown by the fact that artificial insemination shortly after the injection resulted in pregnancy. Successful duplication of these results in the human subject has not yet been reported.

Prolactin, the lactogenic principle of the anterior pituitary gland, is the most recent addition to the list of hormonal preparations advocated for the control of abnormal uterine bleeding. Those reporting good results<sup>19-20</sup> differ as to its probable mode of action. Kupperman and his associates<sup>19</sup> believe its luteotrophic action may account for its apparent beneficial effect. This seems unlikely in view of the fact that these observers could demonstrate no change in the morphology of the endometrium as might be expected if the hormone acted by stimulating luteal function and progesterone secretion. Their observation that prolactin had no demonstrable effect on the length of the cycle, amount of bleeding or morphology of the endometrium in normally menstruating women would also seem to argue against any positive

action of this hormone on the human ovary Goldzieher<sup>20</sup> believes it acts at least partly by suppressing a hypothetical bleeding factor which increases bleeding from the endometrial capillaries. It remains to be seen whether carefully controlled studies will establish the lactogenic hormone as a useful aid or throw it into the discard along with chorionic gonadotropin, which was also once credited with brilliant results in functional uterine bleeding.<sup>21</sup>

On the whole, organotherapy would seem to have only a limited sphere of usefulness in this disorder. In the adolescent, the condition is often self-limited and will eventually correct itself without treatment. In women of child-bearing age, curettage alone, repeated if necessary, is often effective.<sup>22</sup> The gonadotropes should be avoided because of the uncertainty of their action and the danger that they may have a disrupting influence on an already disturbed ovary. Thyroid therapy is often useful, particularly where the basal metabolic rate is depressed. For bleeding during the late reproductive, menopausal and postmenopausal epochs, organotherapy is unnecessary, for radiation or surgery is the therapy of choice and may be resorted to without hesitation at this time of life. Endocrine therapy is not only an unnecessary expense, but if used without a thorough examination to exclude organic lesions, as is often the case,<sup>8</sup> it may cause dangerous delay in the diagnosis and treatment of pelvic carcinoma.

#### AMENORRHEA

Since amenorrhea may result from any one of a number of causes, organic as well as functional, a careful investigation to determine the nature of the underlying disturbance is an essential prerequisite to effective treatment. Unfortunately, a search for the cause is too often subordinated because of the many bold claims that this or that sex hormone is all that is needed to combat the amenorrhea. This attitude is to be deplored, for systemic disease is often overlooked in the rush to apply the sex hormones.

Both the gonadal and gonadotropic hormones have been employed extensively for the treatment of primary and secondary amenorrhea. It is well established that the ovarian sex hormones, if given in adequate amounts over a period of two to three weeks, can develop the human uterine mucosa to the point where cessation of treatment will be followed by bleeding from an estrogenic or progestational type of endometrium, depending on whether estrogen alone or estrogen plus progesterone is used.<sup>23</sup> In some cases, as first shown by Zondek,<sup>24</sup> withdrawal bleeding may be induced by administering progesterone, either alone or with a small quantity of estrogen, on two successive days. Episodes of withdrawal bleeding can be induced at regular intervals as often as the patient's pocketbook will permit. Such treatment is contraindicated where the amenorrhea represents the effort of a depressed organism to conserve its depleted resources. Though the oc-

currence of cyclic bleeding may have a favorable psychological effect on the patient, there is little reason to expect the treatment to correct the underlying ovarian deficiency. Neither estrogen nor progesterone is capable of directly stimulating the hypofunctioning human ovary to normal cyclic function. Observations in the experimental animal and human being suggest that they may indirectly influence ovarian function by way of the anterior pituitary gland. At times, their action is stimulative, at times inhibitory, but the precise conditions under which one or the other effect may be expected have not been defined. Nor is there any evidence which would justify the assumption that the return of normal menses, sometimes seen after sex hormone therapy, is due to its regulatory effect on the anterior hypophysis and is not mere coincidence. Carefully controlled studies, designed to exclude the factor of spontaneous correction and the effect of nonendocrine measures concomitantly employed, are necessary before credence can be given to such claims.

The use of a potent gonadotrope to stimulate the hypofunctioning ovary would seem to have a rational basis and be the therapy of choice where the ovarian depression is secondary to anterior pituitary hypofunction. The available gonadotropins have been employed singly and in various combinations, but the response has thus far been inconstant and unsatisfactory.

Rydberg and Pedersen-Bjergaard<sup>7</sup> employed large doses of equine gonadotropin followed by chorionic gonadotropin in primary and secondary amenorrhea. Increased excretion of estrogen followed by the appearance of pregnanediol, excretion product of progesterone, was demonstrated in one instance during the course of treatment. Its termination was followed by bleeding from a progestational type of endometrium. In another case, the treatment caused marked enlargement of the ovaries due to the formation of lutein cysts, associated with abdominal pain. Davis<sup>8</sup> treated secondary amenorrhea with large doses of "Synapodin," a combination of anterior pituitary extract and chorionic gonadotropin. Some seemed to benefit but others remained unaffected or showed only temporary improvement. It is noteworthy that the best results occurred in amenorrhea associated with obesity. The return of normal periods coincided with loss of weight, which in the author's experience is often sufficient to bring about a return of normal menstrual periodicity. In some of the cases, Davis observed rapid enlargement of the ovaries due to formation of multiple follicles, associated with edema and interstitial hemorrhage. Cyst formation was also noted. The experience of these observers suggests that effective treatment for secondary ovarian hypofunction may eventually become available, but it emphasizes the dangers inherent in the use of gonadal stimulants without precise information as to dosage, timing and the probable reaction of the ovaries in a given case.

Fortunately, the limited usefulness of organotherapy in amenorrhea is not a serious matter, for many cases of amenorrhea, particularly in younger women, are subject to spontaneous correction or respond readily to nonendocrine treatment. Amenorrhea of psychic origin is often self-limited or amenable to psychotherapy.

Of interest is the observation of Whitacre and Barrera<sup>25</sup> that amenorrhea occurred in 14.8 per cent of the women of menstrual age interned at Santo Tomas in Manila. In many of the cases, the menses stopped abruptly either immediately after the first bombing of Manila or shortly after internment and too soon to be attributable to nutritional deficiency. These observers conclude that psychic shock, worry and especially fear were responsible. Hormone studies revealed a deficiency of estrogen associated with normal or possibly excessive quantities of gonadotropin. They suggest that the shock caused amenorrhea by suppressing ovarian function through the mediation of the autonomic nervous system. Most of the women had a spontaneous return of normal periods after a few months. Gonadotropin therapy was withheld because of the positive gonadotropic hormone tests. Sex hormones were not available. For want of something better, vitamin E, which happened to be on hand, was given in doses of 20 drops three times a day for ten days. Eight of ten patients so treated experienced a flow at the end of treatment. Since there is no reason to expect stimulation of the generative tract from such therapy, Whitacre and Barrera assume that the good results were mainly due to its psychotherapeutic effect.

Where the cause of the amenorrhea is a nutritional deficiency, a well-balanced, vitamin-rich diet is often effective, while amenorrhea associated with obesity often responds to reduction of weight through dietotherapy. Small doses of thyroid are a useful adjunct in the treatment, particularly where the basal metabolic rate is low. The use of any metabolic stimulant is contraindicated, however, where the low basal metabolic rate is associated with nutritional deficiency or some other constitutional depressive state, for here it apparently represents an effort of the organism to conserve its waning resources.

#### DYSMENORRHEA

Menstrual pain in the absence of demonstrable pathologic change has long baffled the gynecologist. An endless number of theories have been proposed and equally numerous remedies tried for its relief or cure. Recent evidence suggesting a possible endocrine basis has encouraged the wide use of organotherapy. The reported results have been inconstant and are difficult to evaluate because of the important part played by the psyche in this condition. Confusion arises from the fact that equally good results have seemed to follow opposite forms of treatment, while both good and bad effects have been described after identical therapy. Thus far, a significant advantage of endocrine therapy over general hygienic measures and psychotherapy has not been convincingly demonstrated.<sup>26</sup>

Some observers employ progesterone<sup>27</sup> or pregnenolone<sup>28</sup> with the aim of inhibiting myometrial contractions and promoting the excretion of the motility-stimulating hormone, estrogen. Others oppose this form of treatment on the ground that pain is associated with a pregravid type of endometrium and can be prevented by measures calculated to prevent corpus luteum formation and conversion of the endometrium to the pregravid phase. They reason that progesterone may be expected to aggravate rather than allay menstrual pain. In their

opinion, the use of estrogen<sup>29</sup> or androgen<sup>30</sup> to suppress ovulation and thus prevent painful ovulatory bleeding has a more rational basis. Though there is a growing body of evidence that pain is usually absent during anovulatory menstruation,<sup>31</sup> suppression of ovulation to relieve the dysmenorrheic patient is hardly desirable, particularly in young women. Repeated interference with normal cyclic events in the ovary is not only certain to lower the fertility index but such tampering may disturb the endocrine equilibrium and cause lasting damage. In addition, severe uterine bleeding may sometimes follow estrogen therapy,<sup>31</sup> while the androgens may cause masculinization.

Some observers maintain that uterine hypoplasia is an important etiologic factor in dysmenorrhea and advocate estrogen therapy for its growth-promoting effect, wherever the two conditions coexist. The hormone is administered during the first half of the cycle in relatively small doses to avoid inhibition of ovulation. Jeffcoate, in a recent communication,<sup>32</sup> presents evidence suggesting that this view is unfounded. He concludes that since uterine hypoplasia is not a cause of menstrual pain, estrogen therapy to develop a hypoplastic uterus cannot be expected to relieve an associated dysmenorrhea.

The equine<sup>33</sup> and chorionic<sup>34</sup> gonadotropes have been administered with the aim of directly inhibiting myometrial activity or stimulating luteal function and thus increasing the supply of the motility-inhibiting hormone, progesterone. The earlier enthusiastic reports have recently given way to skepticism.

It is thus apparent that little is to be gained from the use of endocrine products in the treatment of dysmenorrhea. Even where relief from pain is obtained, the price paid, in terms of danger to gonadal function and other undesirable effects, seems too high, particularly since equally good results are obtainable, without danger to the patient, through improved hygiene and psychotherapy.<sup>31 35 36</sup>

#### STERILITY

The value of any form of therapy in sterility is difficult to estimate because the conscientious physician usually employs all the means at his command from which some benefit might reasonably be expected. The possible curative effect of tubal insufflation and endometrial curettage, routinely employed as diagnostic procedures, also tends to obscure the effect of any method of treatment. Of interest in this connection is Sharman's report<sup>37</sup> that among 257 cases of primary sterility, in which insufflation or lipiodol injection of the tubes and endometrial biopsy failed to show any barrier to pregnancy, 116 or 45 per cent subsequently became pregnant without further treatment.

Organotherapy may be resorted to for the treatment of sterility only after excluding or eradicating mechanical obstacles to union of the gametes and nonendocrine faults likely to interfere with egg production.



The estrogens have been employed with the aim of developing a hypoplastic uterus, enlarging the tubal lumen, altering the cervical secretions so as to make them more permeable to the ascending sperm, or modifying the vaginal secretions so as to provide a more favorable medium for the deposited sperm. Unfortunately, the dosage required for these effects is sufficient to inhibit ovulation, an effect which is obviously undesirable where fertility is the main objective.

Administration of a potent gonadotrope capable of inducing normal cyclic changes in the ovary would seem to be rational therapy in sterility due to deficient oogenesis, secondary to anterior pituitary hypofunction. Such a deficiency may exist not only in women with amenorrhea or irregular uterine bleeding, but also in those who have apparently normal flows at monthly intervals. The occurrence of an-ovulatory cycles in such women is now generally conceded, though estimates of their incidence vary widely. In a recent study, Sharman<sup>87</sup> found such cycles in 64 per cent of 358 cases of primary sterility. It is regrettable that the available gonadotropes, in their present form and with the existing limitations on our knowledge concerning their proper application, are of little value and may even do harm in such cases.

There is evidence that with proper control of dosage and timing, ovulation may be induced with gonadotropic substances in the monkey,<sup>38</sup> cow<sup>17</sup> and other species. In the human ovary, the response to similar therapy has thus far been disappointing. Typical is the report of Wilson,<sup>39</sup> who used equine gonadotropin for sterility and at first got results which appeared most encouraging but, in the light of his subsequent experience, proved to be pure coincidence. The ability of the gonadotropes to induce ovulation in the hypofunctioning ovary has not yet been convincingly demonstrated. When brought to bear on ovaries which show some degree of function, they induce alterations which quickly pass the limits of the physiologic. For example, Davis and Hellbaum<sup>40</sup> found that in normally menstruating, pregnant and postpartum women an extract of sheep anterior pituitary gland tissue produced marked enlargement of the ovaries, increasing their size ten to twenty-fold. The proliferative changes thus initiated eventuated in the formation of large follicles and follicle cysts. Except for three pregnant women who appeared to have ovulated just prior to laparotomy, performed following administration of the extract, none of the subjects showed evidence of ovulation or corpus luteum formation.

Equally unphysiologic effects have been described following equine and chorionic gonadotropin given in succession,<sup>7</sup> and anterior pituitary and chorionic gonadotropin administered simultaneously in the form of Synapoidin.<sup>8, 16</sup> Davis<sup>8</sup> observed multiplication of corpora lutea and hemorrhagic follicles with much edema and interstitial hemorrhage and occasionally formation of a single large cyst. According to this observer, these changes occur rapidly but regress slowly. In some of his cases several months passed before the ovaries returned to normal size. He points out that such tumors are liable to the general risks of complications such as hemorrhage and torsion, and call for careful supervision during treatment.

It is to be hoped that proper control of dosage and timing will eventually make it possible to avoid these undesirable effects. For the present, however, these substances should be used with caution because

of their possible disrupting influence. Reports of severe allergic reactions<sup>41</sup> emphasize the need for care. Evidence that antigonadotropin formation may follow their protracted administration<sup>42</sup> further detracts from their value as ovarian stimulants.

### HABITUAL AND THREATENED ABORTION

Evidence that endocrine factors play an important role in the maintenance of gestation and its successful termination has led many clinicians to resort to organotherapy in cases of habitual and threatened abortion. Progesterone or pregnenolone is employed<sup>43</sup> because of its ability to maintain the nidatory bed and its quiescent effect on the myometrium. Both large and small doses have been tried but there is as yet no convincing proof that the results are significantly better than those with bed rest, sedation and other nonendocrine measures.<sup>44</sup> Some observers believe progesterone is of little value and, in large doses, may even aggravate a tendency to abortion by depressing the metabolism of intrinsic progesterone.<sup>45</sup> Another possible disadvantage of progesterone therapy is suggested by Murphy's<sup>46</sup> report of prolongation of pregnancy and excessive fetal development after progesterone administration for habitual abortion. A fair evaluation of this form of treatment must await improved methods of establishing progesterone deficiency and excluding the numerous other factors, of maternal and fetal origin, which may play a part in the etiology. Recent studies suggesting that the Rh factor may account for some cases of abortion<sup>47</sup> emphasize the complexity of the mechanism concerned in the maintenance of pregnancy and serve as a reminder that we should not be too hasty in tagging a case as endocrine in origin and treating it accordingly.

Estrogen has also been advocated<sup>48</sup> for use where hormonal tests of the body fluids reveal low titers of this hormone. In view of evidence that estrogen may have an abortifacient action under some circumstances, it should be used with caution. It must be emphasized that our understanding of the mechanism controlling the hormone levels in the blood and urine during pregnancy is still incomplete. In the present state of our knowledge, we cannot be certain that low estrogen titers denote deficient production rather than increased utilization of an adequate supply. Indeed, low estrogen titers may even conceivably signify increased conversion or destruction, representing an effort of the organism to rid itself of the hormone. So long as the interpretation of these findings remains uncertain, therapy based thereon is necessarily empirical and should our guess be wrong, more harm than good may follow.

Prolactin has been given a trial in threatened abortion,<sup>49</sup> but the number of cases is still too limited to permit any judgment as to its efficacy.

I have reached the conclusion that general hygienic and medical measures calculated to put the patient into the best possible physical and mental state are to be preferred. Thyroid therapy is of value where the basal metabolic rate is low or fails to show the usual rise with the advance of gestation.<sup>49</sup> Where abortion threatens, rest in bed, mild sedation and avoidance of coitus, purgatives and undue excitement would seem to be as effective as any other form of therapy thus far proposed.

### THE CLIMACTERIC

Before attempting to pass judgment on the rationality or efficacy of any form of treatment recommended for the relief or cure of the climacteric symptom complex, it is important to bear in mind that it is an expression of a general nervous and endocrine upheaval, possibly precipitated by the decline of ovarian function. The nature, intensity and duration of the symptoms apparently depend on the severity of this upheaval and the reaction of the organism to the altered hormonal and nervous environment. This in turn depends on the previous status of each system and the extent to which it is implicated in the general regression which heralds the approaching senium. Since aging and ovarian regression are inevitable and irreversible processes, it is obvious that no form of therapy can do more than ease the patient through this critical epoch.

Sex hormones, particularly the estrogens,<sup>50, 51</sup> have achieved their greatest popularity in the treatment of the vasomotor and other annoying symptoms associated with the menopause. Even those who have maintained an attitude of cautious skepticism regarding their value in menstrual and reproductive disorders, have permitted themselves to become enthusiastic concerning their use for this purpose.

The degree of the enthusiasm for estrogenic therapy in the menopause varies. Some find the estrogens effective only for the control of flushes, while others claim good results in a variety of conditions including kraurosis vulvae, arthritic pains, intestinal symptoms, hypertension, edema, hyperglycemia and glycosuria, respiratory and circulatory disturbances, dysuria and incontinence, and involutional melancholia. Since gonadal involution with consequent estrogen withdrawal is only one of many physical and psychological changes incident to the aging process, it is difficult to conceive how mere substitution of estrogen can relieve or control the complex symptomatology. In view of the large component of psychosomatic manifestations associated with this epoch, it is entirely possible that the brilliant results attributed to estrogen therapy are in large part due to its psychotherapeutic effect. It is significant that many menopausal women are relieved by reassurance, alone or with sedation,<sup>52</sup> and often respond to placebos. Of interest in this connection is Frank's observation<sup>53</sup> that oral estrogen therapy, which relieved most of his patients, was without effect in a few who had convinced themselves that estrogen by this route is ineffective. If it is granted that a patient's psychic convictions can prevent her from responding to estrogen therapy, one cannot help but suspect that favorable responses, where noted, were due to the psychic conviction that the therapy would be effective.

Aside from the fact that its superiority over placebos has not been convincingly established, estrogen therapy has several disadvantages. In the woman whose menses have already ceased, the hormone may induce bleeding and compel the clinician to perform curettage in order to determine whether the hemorrhage is due to the treatment or to a lesion which has developed during its course. The danger of stimulating a latent tendency to malignancy, though not definitely proved, nevertheless merits serious consideration since there is as yet no conclusive evidence that the human being is immune to the carcinogenic activity of estrogen. Even if it is conceded that estrogen gives relief, it is at the price of postponing the complete weaning of the organism from the need for this hormone. Whether its effect is physiological, psychological or a combination of both, its continued administration may make the patient dependent on it long after she would normally require it, were treatment withheld.

Androgen therapy for the relief of menopausal symptoms is based on its supposed ability to inhibit a hyperactive anterior pituitary, which is presumably contributing to the symptoms. The danger of inducing masculinization, particularly at this time of life when a tendency to hirsutism is not uncommon, detracts from its value. As in the case of estrogen, the possibility that the relief obtained is due to the psychological rather than the physiological effect of the treatment cannot be ignored.

To the author, who has always favored general hygienic measures combined with reassurance, sedation and psychotherapy,<sup>52</sup> it is indeed gratifying to observe that the trend among careful observers, as evidenced in a recent symposium,<sup>53, 54, 55</sup> is to emphasize treatment of the patient as a whole and particularly her psyche as the primary consideration, giving organotherapy a secondary and at best only a minor position in the therapeutic armamentarium.

In addition to the entities discussed above, numerous other conditions have been treated at one time or another with the sex hormones. The estrogens have been used to induce labor or stimulate it in uterine inertia, to suppress postpartum breast engorgement, and to control gonorrheal vulvovaginitis in children, senile vaginitis, kraurosis vulvae, pruritus vulvae, migraine headaches, vomiting of pregnancy, premenstrual tension, premenstrual mammary pain and chronic mastitis, frigidity, acne and hirsutism. Limitations of space prevent a detailed discussion of their value in these conditions. Briefly stated it is very limited and, in some of the entities listed, highly questionable. In none has it been conclusively shown to excel other nonendocrine measures.

#### BIBLIOGRAPHY

- 1 Woodruff J D and Te Lende, R W: *South Med J.*, 35:389 1942.
- 2 Novak, E. *J.A.M.A.*, 125:98 1944

- 3 Scheffey, L C, Farell, D and Hahn, G A J.A.M.A., 127 76, 1945
- 4 Hertig, A T J Clin Endocrinol, 4 581, 1944
- 5 Brown, W E., Bradbury, J T, and Metzger, I Am J Obst. & Gynec., 41 582, 1941.
- 6 Hartman, C G J Clin Endocrinol, 5 99, 1945
- 7 Rydberg, E and Pedersen-Bjergaard, K J.A.M.A., 121 1117, 1943
- 8 Davis, A J Obst. & Gynec Brit Emp., 51 401, 1944
- 9 Heller, C G, Farney, J P., Morgan, D N and Meyers, G B J Clin Endocrinol, 4 95, 1944
- 10 Allen, W M and Heckel, G P Am J Obst. & Gynec, 44 984, 1942
- 11 Gaines, J A., Geist, S H and Salmon, U J J Clin Endocrinol., 1 554, 1941
- 12 Hamblen, E. C., Cuyler, W K., Hirst, D V and Horner, V O J Clin Endocrinol., 2 369, 1942
- 13 Hamblen, E. C., Hirst, D V and Cuyler, W K. Am J Obst & Gynec., 45 513, 1943
- 14 Abarbanel, A R Am J Obst & Gynec., 39 243, 1940
- 15 Hamblen, E C Am J Obst. & Gynec., 40 615, 1941
- 16 Mazer, C. and Ravetz, E Am J Obst & Gynec, 41 474, 1941
- 17 Casida, L E., McShan, W U and Meyer, R K J Animal Sc, 3 273, 1944
- 18 Hall, G J J Clin Endocrinol., 2 296, 1942
- 19 Kupperman, H S., Fried, P and Hair, L Q Am. J Obst & Gynec., 48 228, 1944
- 20 Goldzieher, M A J Clin Endocrinol., 5 132, 1945
- 21 Jeffcoate, T N A J Obst. & Gynec Brit Emp, 44 31, 1937
- 22 Jones, G E. S and Te Linde, R W Bull J Hopkins Hosp., 71 282, 1942
- 23 Neustaedter, T Am. J Obst. & Gynec., 38 609, 1939
- 24 Zondek, B J.A.M.A., 118 705, 1942
- 25 Whitacre, F and Barrera, B J.A.M.A., 124 399, 1944
- 26 Boynton, R E and Winther, N J.A.M.A., 119 122, 1942
- 27 Kurzrok, L., Birnberg, C. H and Livingston, S Am J Surg., 46 353, 1939
- 28 Soule, S D J Clin Endocrinol., 1 567, 1941
- 29 Sturgis, S H and Meigs, J V Surg, Gynec & Obst, 75 87, 1942
- 30 Cinberg, B L New York State J Med., 42 2138, 1942
- 31 Randall, J H and Odell, L D J.A.M.A., 123 735, 1943
- 32 Jeffcoate, T N A J Obst. & Gynec Brit. Emp., 52 97, 1945
- 33 Gray, L A. Am J Obst. & Gynec., 43 387, 1942
- 34 Shute, E. V Canad M A J., 42 145, 1940
- 35 Wengraf, F Am J Obst. & Gynec., 48 475, 1944
- 36 Kroger, W S and Freed, S C Am J Obst. & Gynec, 46 817, 1943
- 37 Sharman, A J Obst & Gynec Brit. Emp., 51 85, 1944
- 38 Pfeiffer, C A Anat Rec., 91 295 (Abst), 1945
- 39 Wilson, W M West J Surg, 50 6, 1942
- 40 Davis, M E. and Hellbaum, A. A J Clin Endocrinol, 3 517, 1943, *ibid.*, 4 400, 1944
- 41 Phillips, E. W Am J Obst. & Gynec, 44 706, 1942
- 42 Leatham, J H Endocrinol., 36 67, 1945, J Clin Endocrinol., 4 500, 1944
- 43 Allen, E. Am J Obst. & Gynec., 46 70, 1943
- 44 Wenner, cited in Helvet. Med Acta., 10 435, 1943
- 45 Hamblen, E C Am J Obst. & Gynec., 32 110, 1936
- 46 Murphy, D P Am. J Obst. & Gynec., 47 697, 1944
- 47 Cohn, T D and Cole, S L Am J Dis Child, 68 28, 1944
- 48 Turunen, A. Wien med Wehnschr, 93 115, 1943
- 49 Bloss, J R South Med J., 30 637, 1937
- 50 Harding, F E Am J Obst. & Gynec., 48 181, 1944

- 51 McElroy R. C. Urol. & Cutan. Rev., 48 124, 1944
- 52 Buxton, C. L. J Clin Endocrinol., 4 591 1944
- 53 Frank, R. T. Am J Obst & Gynec., 47 561, 1944
- 54 Watson B. P. J Clin. Endocrinol., 4 571 1944
- 55 Engle, E. T. J Clin. Endocrinol., 4 567, 1944
- 56 Hoffman, J. Female Endocrinology Including Sections on the Male. Philadelphia, W. B. Saunders Co., 1944

## DYSMENORRHEA

EDWARD H BISHOP, M D \*

DYSMENORRHEA is one of the most common of all gynecologic complaints and is experienced to some degree by at least 50 per cent of all women. In spite of its frequency it still remains one of the most difficult problems to treat satisfactorily. The greatest complicating factor is that dysmenorrhea is a symptom and, unfortunately, is a symptom of not one but many varying pathologic conditions. In order to treat this symptom with any degree of success the etiology must first be determined and the problem approached in a logical manner. Too often dysmenorrhea is treated as a disease entity and too often it is treated on an empirical basis. Since this only too frequently results in failure, dysmenorrhea is often relegated to that group of discomforts which must be tolerated rather than relieved. Therefore it seems best to discuss the management by first considering the various types and causes. In this way one may develop a rational and logical consideration of the treatment.

### DIAGNOSIS

Dysmenorrhea may be divided into primary and secondary types. When some demonstrable pelvic disturbance is present with dysmenorrhea as a symptom, it is classified as *secondary* dysmenorrhea. When no abnormality can be detected in the genitalia to account for the pain it is known as *primary* or *functional* dysmenorrhea. Since secondary dysmenorrhea is usually easier to diagnose and easier to treat it seems best to search for any of the possible causes for this type as the first step in the management of this problem.

The initial procedure undertaken in order to determine the etiology is a careful history and complete physical examination. In addition to the usual gynecologic history the physician should obtain a detailed history of the menstrual pain, the age at which it first occurred, the time relationship to the menstrual period, the location and radiation of the pain and recent changes in the intensity of the pain. These details often serve as valuable clues to the final diagnosis. As examples, the menstrual cramps which are primary in type usually first occur early in life, do not increase with age and occur in the early part of the menstrual period, the dysmenorrhea associated with endo-

---

From the Department of Gynecology, Jefferson Medical College, and the Pennsylvania Hospital, Philadelphia

\* Instructor in Gynecology, Jefferson Medical College, Clinical Assistant in Gynecology and Obstetrics, Pennsylvania Hospital, Assistant in Gynecology and Obstetrics, Methodist Hospital

metriosis first appears later in life, is "boring" in character, gradually increases with succeeding periods and is usually present during the entire menstrual period, while the dysmenorrhea associated with pelvic inflammatory disease first appears following infection with tubal involvement, is dull and aching in character and is felt in the lower lumbar region and lower abdomen

The history and general physical examination should be followed by a complete and thorough pelvic examination. At this time one may find evidence of any of the various pelvic abnormalities which may cause secondary dysmenorrhea. These conditions are most often endometriosis, pelvic inflammatory disease, uterine fibroids, ovarian cysts, endocervicitis, cervical and uterine polyps and, occasionally, displacements of the uterus. The diagnosis of all of these is usually easy to make and is not within the province of this discussion.

#### TREATMENT OF SECONDARY DYSMENORRHEA

The treatment of the various conditions responsible for secondary dysmenorrhea has been well established and need not be repeated here. The proper and adequate treatment of the primary condition will serve to eradicate the dysmenorrhea. It is well to remember that not only the obvious but any and all pelvic diseases or abnormalities should be treated since more than one factor may be the cause of the symptoms.

The one cause of secondary dysmenorrhea which is most frequently overlooked is *endocervicitis*. This diagnosis cannot be made by visual inspection alone, frequently it is necessary to insert a probe or sound into the cervical canal to or past the level of the internal os. Very often, associated with endocervicitis, one will find an obstruction of the cervical canal just below the level of the internal os, dilatation of which will relieve the dysmenorrhea. It is characteristic that when this dilatation is performed the patient will experience the same type of pain which she experiences at the time of the menses. Both the insertion of the sound and the dilatation (if it is not too painful) can be carried out safely as an office procedure if one uses sterile instruments and cleanses the vagina first with some efficient, nonirritating antiseptic solution. The 1:1000 aqueous solution of benzyl-trialkonium chloride serves this purpose very well. If such a stricture is present an office dilatation usually serves to alleviate the pain for a period varying from two to eight months, after which time it can be repeated. If desired, or if it is necessary, a more thorough dilatation can be performed under anesthesia and by using either Goodell or Hegar cervical dilators. In certain selected cases a stem pessary can be inserted and left in place through two menstrual periods, giving a more permanent relief.

By emphasizing endocervicitis as a cause of dysmenorrhea I do not wish to imply that it is the most common cause but in the swing of



the pendulum of opinion away from the mechanical theories many of these milder cases of endocervicitis with stricture are overlooked. Supplementing the dilatation of the cervical canal, treatment should be directed toward other evidences of endocervicitis such as eversion, nabothian cysts and ectropion. Cauterization or coagulation offers the best method of treatment and if done lightly and carefully one does not need fear further stricture as a result.

In a small group of cases it has been found that ureteral strictures or ureteral abnormalities may be the cause of the pain at the time of the menstrual period. In any case in which urinary symptoms are present a complete urologic investigation is indicated.

Among the laboratory procedures which are sometimes helpful are determination of the red cell count, hemoglobin and basal metabolism. Mild anemia and hypothyroidism are not prominent among the causes of secondary dysmenorrhea but may often be contributing factors.

#### TREATMENT OF PRIMARY DYSMENORRHEA

After one has searched for and removed the causes of secondary dysmenorrhea, there still remains the very large group of cases in which one can find no physical basis for the symptoms—the so-called primary or functional type of dysmenorrhea. Many theories have been advanced to explain the pain experienced by this group of patients, but without agreement. As yet no offered concept fits all cases and, therefore, they must be treated on a more or less empirical basis. Undoubtedly there is a large psychic element present in all of these cases which results in a marked lowering of the pain threshold. Nevertheless, these patients cannot be dismissed as “neurotic” but instead one must find some method of relieving their pain. It seems best to treat these patients in the following order:

1 **General Measures**—Good physical and mental hygiene should not be forgotten as part of our therapeutic armamentarium. Clow has reported that she was able to reduce the incidence of dysmenorrhea in a girls' school 70 per cent by having the girls take warm showers and moderate exercise during their menstrual periods, by using laxatives as indicated and by placing them on a proper, well balanced diet.

The nature of the complaint should be explained to the patient in detail. She must be made to realize that menstruation is a normal function and that normal activities should be maintained during this time. The patient who anticipates a debilitating period and prepares for it by incapacitating herself before the actual pain appears usually fulfills her anticipations.

2 **Analgesics, Antispasmodics and Heat**—The use of one of the many analgesics (acetylsalicylic acid, phenacetin, and so forth) and light sedation still remain as the most satisfactory method of treatment for the milder cases. The various antispasmodics (including the synthetic

and proprietary antispasmodics) are of dubious value and do not prove satisfactory in spite of the enthusiasm and wide publicity given them by the various commercial drug concerns. Kymographic studies, when carefully done, have failed to show that any of these have much effect in relaxing the myometrial contractions. The successes which have been reported were probably due to the psychotherapeutic effect of the administration and attention. This power of suggestion was well illustrated by a group of approximately 1000 women treated under my direction during their hours of employment. Most of these women were relieved of their menstrual pain by a mild analgesic when administered in the accustomed green tablet but when given the same medication in a white tablet only 30 per cent of the previous number experienced relief and the time loss due to dysmenorrhea was markedly increased. This increase promptly diminished when the same medication was again offered in the standard form originally used. The same results were experienced when an antispasmodic was used instead of the analgesic tablets.

Heat in any of its forms of application, whether taken internally as a hot drink or warm enema, or whether applied externally in the form of a heating pad, hot water bottle or hot bath, gives a definite sensation of relief.

Benzedrine may be included in this group of therapeutic aids. In spite of the glowing reports in the literature any benefit which it has is probably due to its ability to raise the pain threshold. The side reactions and the possibility of habit formation make it an unsatisfactory drug for continued use.

3 Endocrine Treatment—All of the many types of endocrine products have been used for the treatment of dysmenorrhea—anterior pituitary like substance, gonadotropins, estrogens, progesterone and androgens. However when endocrine studies have been made on patients with dysmenorrhea there have been no definite and repeated abnormalities in the levels of estrogens, progesterone or androgens, either deficiency or excess. Originally it was thought that progesterone would prove of value because of its relaxing effect on the myometrium but the clinical results with this product have not proved satisfactory.

The products which have proved of greatest value are the estrogens and androgens. The basis of treatment with both is that dysmenorrhea occurs only when ovulation has occurred and does not occur during an anovulatory period. Therefore, by the administration of estrogenic or androgenic substances during the early part of the menstrual cycle one may inhibit ovulation and thereby prevent pain at the time of the menstrual period. The easiest and most efficacious method of doing this is by the administration of 1 mg. of stilbestrol daily for 20 doses beginning at the onset of a menstrual period. This may be repeated during the following cycle and then followed by one or more periods of rest. The natural estrogenic products such as estradiol dipropion-

ate, estriol glucuronides, ethynyl estradiol, estrone and estradiol benzoate may be used in comparative dosages large enough to inhibit ovulation. Nevertheless stilbestrol is the drug of choice because of its comparative low cost, its effectiveness and the simplicity of its administration. The natural estrogens may be used when the toxic effects, such as gastrointestinal disturbances, prevent the use of stilbestrol.

The use of testosterone propionate is based on the same concept as the use of the estrogenic substances, namely the inhibition of the gonadotropic factor of the pituitary with the subsequent suppression of ovulation followed by an anovulatory menstrual period which is usually free of pain. This drug is not as safe as the estrogens because the therapeutic dose may approach the dose which results in masculinizing changes.

The endocrine treatment of dysmenorrhea should be undertaken with the greatest of caution. It should be employed only in selected cases and then only for short periods of time. Even though we may relieve the patient symptomatically, the cure is only temporary and as yet we do not know the late effects on the endocrine system due to the administration of these products over long periods of time. We may permanently interfere with ovulation or at the least seriously disturb the delicate endocrine balance. As long as this is a possibility it does not seem justifiable to use this method of treatment until all other forms have been exhausted.

4 **Exercise**—Adams, and more recently Billig, have proposed the thesis that dysmenorrhea may be caused by a postural defect resulting in contracted ligamentous bands of the pelvic fascia. Billig states that at the time of menstruation, due to the action of the ovarian hormones, there is a further shortening of these bands resulting in an irritation of the spinal nerves passing through and by them. He has devised some simple exercises which result in a gradual lengthening of the ligaments involved, thus freeing the nerves from their impingement. The results published by Billig and others have been quite encouraging. Recently Haman has corroborated these findings and suggested a modification and simplification of the exercises devised by Billig.

5 **Hypnosis**—Hypnosis has been used satisfactorily in a small series of cases but the field of its usefulness is limited by the necessary selection of cases and the scarcity of competent and interested psychiatrists. The results are probably due to a raising of the pain threshold by posthypnotic suggestion.

6 **Neurological Treatment**—After all of the above methods of treatment have been used there still remains a group of patients who have intractable and incapacitating pain at the time of the menses. For these, the only remaining treatment is surgical, by the performance of a resection of the superior hypogastric plexus or the presacral nerve. The results of this operation are quite satisfactory when the cases have

been carefully selected and when carried out by experienced operators. The disturbing side effects are few but certain factors militate against it. First, it carries a certain element of danger as does any abdominal operation. Second, all back pain may not be relieved. Third, in some cases there is an interference with satisfactory coitus. There is no interference with pregnancy and no change in bladder or bowel function.

### CONCLUSIONS

When reviewing the literature on the treatment of dysmenorrhea one must approach the results very critically. The methods of treatment offered are many and diverse but almost every author reports from 50 to 90 per cent cure for his pet method of treatment. From a practical aspect it appears that the best methods of treatment available without endangering the patient are the milder analgesics, dilatation of the cervix and special exercises. Endocrine treatment should be used cautiously and only temporarily. Presacral sympathectomy should be reserved for those severe cases which cannot be relieved by other forms of treatment.

## THE MENOPAUSE

JOHN B. MONTGOMERY, M.D., F.A.C.S.\*

THE word "menopause" literally refers to cessation of the menstrual function. However, it is commonly used interchangeably with the broader term "climacteric" which denotes that transitional period in the life of woman characterized by ovarian failure, loss of the child-bearing function, cessation of the menses and regressive changes in the genitalia.

Menstruation usually ceases between the ages of 40 and 50, the average being about 47. When the menopause occurs earlier it is usually due to surgical removal of the ovaries, radiation therapy, prolonged lactation or some endocrine disturbance which is associated with a lack of ovarian function. However, in occasional instances which are often influenced by heredity, the menopause may occur spontaneously at an early age. In about 10 per cent of women menstruation does not cease until after the fiftieth year and occasionally the menopause is delayed until 55. Although normal menstruation has occasionally been noted beyond this age, such an occurrence should always be investigated by diagnostic curettage and cervical biopsy to rule out uterine malignancy or an ovarian tumor, even though the cycles are reported to be normal.

The menopause is an integral part of the process of aging, in no sense can it be regarded as a disease. However, the profound changes that occur in physiologic processes and in physical structure, together with associated emotional and nervous disturbances sometimes are responsible for annoying symptoms. On the other hand these changes, together with the freedom from menstrual distress and from fear of pregnancy at times result in marked improvement of general health, increased vitality, and a sense of well-being beyond anything that the individual has experienced during her active menstrual life.

### ETIOLOGY

**Endocrine Changes**—The underlying cause of the menopause and its associated phenomena is failure of ovarian function with its related endocrine disturbances. This is apparently due to the normal aging of the ovary which causes it to become refractive to the gonadotropic hormone of the anterior pituitary. Failure of ovulation is probably the

---

From the Department of Gynecology, Jefferson Medical College, Philadelphia.

\* Clinical Professor of Gynecology, Jefferson Medical College, Assistant Gynecologist, Jefferson Medical College Hospital, Assistant Attending Obstetrician, Bryn Mawr Hospital, Bryn Mawr, Pennsylvania.

first break in the endocrine cycle. This may occur abruptly or ovulation may recur at increasingly long intervals until it ceases completely. Failure of ovulation is followed by absence of the corpus luteum with its progestational influence. This defect may begin some months or even a year or more before menstruation ceases in which case the monthly bleeding is spoken of as anovulatory menstruation. Although during this phase the ovary fails to respond to the luteinizing gonadotropic hormone (prolan B) it may continue to be activated by the follicle-stimulating hormone (prolan A) so that graafian follicles continue to develop. This results in an excess of the follicular hormone (estrogen) and has been spoken of by Zondek as the polyfolliculin phase. It is during this time that abnormal bleeding is likely to occur due to fluctuations in the amount of estrogen in the blood. Finally the ovaries become incapable of responding to the pituitary influence and estrogen formation in the ovary ceases completely, although a small amount may continue to be produced by the adrenal cortex.

As the production of ovarian hormones wanes, their cyclical restraining influence on the anterior pituitary ceases and large amounts of gonadotropic hormones appear in the blood and urine. This is spoken of by Zondek as the polyprolan phase of the menopause. Whether this increase is due to a greater production of hormone by the anterior lobe of the pituitary or to failure of the ovaries to utilize it is uncertain. Its importance lies in the fact that the excess of gonadotropins is probably the prime factor in the production of many of the menopausal symptoms. This effect is probably brought about by the direct influence of the gonadotropic hormones upon other endocrine glands, notably the thyroid, adrenals and pancreas, and also by virtue of the little understood relationship of these hormones to the nervous system. The similarity between certain manifestations of the menopause (tachycardia, tremors, emotional instability, etc.) and the symptoms of hyperthyroidism is well recognized. Increased hair growth and other masculinizing changes are attributed to increased production of the male hormone (androgen) by the adrenals. The frequent occurrence of diabetes and other evidences of disturbed carbohydrate metabolism during the climacteric suggests that the pancreas also is affected by the disturbance in pituitary function. In course of time, the hormonal balance is restored spontaneously, the hyperactivity of the anterior pituitary returns to normal and the high concentration of gonadotropic hormones disappears from the blood and urine. The menopausal epoch or the climacteric has passed.

**Nervous and Emotional Influences.**—To women generally the menopause brings an acute awareness of advancing years. The fear of malignancy, cardiovascular, mental and metabolic diseases, the lack of economic security, apprehension that menopausal changes will make them less attractive to their husbands, together with the over-reaction of the sympathetic nervous system which often results in symptoms

that are alarming to the patient, frequently creates a marked state of anxiety. This in itself may be responsible for many of the most distressing symptoms. These influences are likely to be especially damaging to the woman with marked psychoneurotic tendencies. On the other hand, although the symptoms of organic mental disease may be precipitated at the time of the menopause there is no evidence to indicate that psychoses are actually produced by failure of ovarian function.

**Physical Changes**—General physical changes are usually emphasized by the tendency to gain weight and particularly by the deposit of fat over the hips and girdle region. In some women these changes result in refinement of contour and increase in appearance of general good health which enhances their physical attractiveness. Regressive changes in the genital system begin after the estrogenic influence wanes. The endometrium becomes thin, the uterus becomes small and firm due to the atrophy of the myometrium and the development of fibrous tissue. The vaginal mucosa decreases in thickness (atrophic vaginitis, senile vaginitis) and the underlying supportive tissues undergo atrophic changes that sometimes result in shortening and deformity of the canal. The cervix decreases in size and at times may be hidden from view because of contraction of the vaginal vault and adhesions of the vaginal mucosa. These changes also affect the endopelvic fascia so that inherent weaknesses are exaggerated and become manifest in the development of uterine prolapse, cystocele or rectocele. The external genitalia decrease in size. The mons becomes less prominent, the small labia shrink, the pubic hair becomes sparse and the mucous membrane becomes smooth and pale. Areas of leukoplakia are common and at times atrophic changes are extreme, resulting in kraurosis vulvae. In spite of these changes the vulvar glands may continue to secrete mucus, and sexual sensations and libido may be unimpaired. The atrophic changes in the genital system may also affect the urethra and neck of the bladder resulting in urinary frequency or stress incontinence. Atrophy of the breasts may be a prominent feature although this is sometimes disguised by deposition of fat.

#### SYMPTOMS

It is generally conceded that the great majority of women go through the menopause without symptoms which are severe enough to interfere with their general welfare. However, with the advent of hormone therapy and the free discussion of this problem in the lay press an increasing number of women are consulting their doctors for relief of symptoms which they attribute to the menopause. In dealing with this ever-enlarging group of patients it is well to remember that symptoms which are attributed to the menopause frequently may be due to underlying organic disease. Severe menopausal symptoms will be encountered in only about 10 per cent of the patients.

**Menstrual Disturbances**—In a few women the menses stop abruptly, more frequently the flow becomes shorter in duration and more scant, with an increasingly prolonged interval until it finally ceases altogether. Postmenstrual staining, bleeding between periods or increased or prolonged flow which occurs so frequently at this time is never normal. It is always suggestive of malignancy and demands *immediate* investigation, including careful pelvic examination, diagnostic curettage and cervical biopsy. In no instance should such a patient be treated with hormones before such a thorough investigation is carried out. Failure to make such examinations will not infrequently result in delay in the diagnosis of malignancy. Such delay is inexcusable and may cost the life of the patient.

**Circulatory Symptoms**—Hot flushes are the most constant symptoms. Characterized by a sensation of heat referred to the head and neck, associated with flushing of the face, and often followed by a profuse sweat, they may last from a few seconds to several minutes. They may occur long before and persist long after the menstrual periods have ceased. In many instances they are mild and occur only when the patient is excited, while in some they occur every few minutes day and night causing much general agitation and interfering with sleep. The attacks are often accompanied by palpitation, weakness, vertigo and other vasomotor symptoms that add greatly to the patient's distress.

Elevation of the blood pressure which is common at this age is likely to be aggravated. Extreme fluctuations are frequent and many clinicians have come to regard the disturbed physiology of the menopause as an important etiologic factor in many of these patients.

**Nervous Symptoms**—Symptoms of nervous origin are common and may occur in great variety, especially in women of psychoneurotic tendencies. Many of these are referred to the skin. Pruritus, commonly localized in the vulvar or anal regions, may occur in any area and is generalized at times. Paresthesia, hyperesthesia and neuralgia are frequent. Headaches are often greatly exaggerated. Their origin is uncertain but in some instances they may be associated with disturbances in the pituitary. More commonly they are probably influenced by variation in the blood pressure and by the emotional tension associated with anxiety. Vertigo is very common as are insomnia, fatigue, extreme weakness and emotional instability.

Functional gastrointestinal disturbances are often greatly exaggerated and frequently necessitate thorough gastrointestinal study in order to rule out organic disease.

**Arthritis**.—Many clinicians now agree that a mild form of arthritis which especially affects the knees may result from menopausal disturbances. Others point out that these lesions occur most frequently in women who have gained much weight and are most likely due to trauma incident to weightbearing.



## DIAGNOSIS

In dealing with the menopausal woman, a thorough survey of the patient is absolutely essential before her symptoms can be evaluated and a sound rational plan of treatment can be outlined. The problems of differential diagnosis presented by the multiplicity of symptoms are often very complex and may tax the ability of the most experienced physician. One is never justified in assuming that the symptoms are functional in origin. A complete history and a complete physical examination are essential. This should include careful examination of the breasts, bimanual examination of the pelvis, inspection of the vagina and cervix through a speculum, digital palpation and proctoscopic examination of the rectum. A blood count and urinalysis should always be made. Basal metabolism determination, electrocardiogram, evening-ground study, blood chemistry, gastrointestinal x-ray and the like should be carried out promptly if suggestive symptoms are present. Such a thorough study is really an important part of treatment. It will go far toward allaying the patient's anxiety and increasing her confidence in the opinions and advice of her doctor.

## TREATMENT

In treating the menopausal patient, the physician must be ever conscious of the fact that the physiologic disturbances that produce the characteristic symptoms and physical alterations are due to the normal process of aging, and therefore cannot be prevented or reversed. It is important also to recognize the influence of the patient's nervous temperament, emotional instability, and her anxiety which is so often secondary to fears which arise from a lack of understanding of the true significance of the menopause.

Treatment should always begin with a simple, brief explanation of the phenomena underlying the menopause and of their significance. The patient should clearly understand that she is in no unusual danger of serious physical or mental illness. She should realize that rather than a portent of imminent old age, the menopause is nature's way of freeing her from the annoyances of menstruation and the hazards of pregnancy and childbirth at an age when she can live for many more years in the vigor of good health. A few minutes spent in simple explanation plus the assurance that results from a careful complete physical examination goes a long way toward alleviating the anxiety that underlies many of the menopausal symptoms. In many cases no further treatment is necessary.

**General Measures**—In most instances, general medical measures should be tried before instituting endocrine therapy. Measures to improve the general hygiene of living are very helpful. Many women suffer from overwork and lack of sleep. The cares of family life are heavy upon them. Faulty diet, with excesses of coffee and cigarettes, are not uncommon. Constipation, anemia and obesity are frequent

The latter although often due to overeating is not uncommonly influenced by the endocrine disturbances and in addition to dietary restriction may require special measures for its control.

General sedation with phenobarbital is invaluable. In small doses three times daily and increased to 1 or  $1\frac{1}{2}$  grains at bedtime, it is often the only medication that is necessary. At times one of the more rapidly acting barbiturates is preferable at night. Since sedation is often required over a prolonged period of time, bromides are not advised. Addiction to barbiturates should be guarded against by using small doses, administered in cycles which should be shortened and discontinued as soon as possible.

**Endocrine Therapy**—The rationale of estrogen therapy in the menopause is now accepted generally although there are some who question its value. It is pointed out that the psychoneurotic nature and the emotional instability of many patients make it difficult to evaluate the effects of treatment since much of the improvement may be due to the psychotherapeutic effect. Those who question the wisdom of estrogen therapy also emphasize many dangers, although it is admitted that most of these are theoretical and have not been proved. Hoffman states that in his experience general medical measures, reassurance, sedation and hypodermic injection of sterile saline solutions used for psychotherapeutic effect, have proved more efficacious than the estrogens or other hormonal preparations in the vast majority of cases. Both Hamblen and Novak emphasize the value of general medical measures, sedative, psychotherapy, and so forth, but point out the great value of estrogen therapy in those women who suffer from severe vasomotor symptoms. The aim in such treatment is not to overcome an estrogen deficiency indefinitely but to provide a gradual withdrawal that will enable the body to adjust itself more slowly. Endocrinologists generally agree that the best that can be expected from estrogen therapy is palliation of the most distressing symptoms.

**DANGERS OF ESTROGEN THERAPY**—It is well known that very large doses of estrogenic hormones will induce the development of malignant tumors in susceptible laboratory animals. Although the dose used in experimental animals is, in proportion, many times greater than the clinical dose, the possibility of influencing the development of cancer in women of menopausal age must be kept in mind. However, no definite evidence has been produced to prove that estrogen therapy can induce malignant disease in humans.

It is rather generally agreed that the prolonged use of estrogens is unphysiologic and may have harmful effects. It is very probable that the relief of vasomotor symptoms is due to depression of the production of gonadotropic hormone by the anterior pituitary. Possibly this depressing effect may involve the pituitary influence on other endocrine glands, notably the thyroid and the adrenal and thereby further interfere with normal endocrine balance. Prolonged estrogen

treatment may possibly delay the climacteric and simply "put off the evil day." Speaking of intensive estrogen therapy, Hamblen states that "the entire orderly process of sexual aging may be frustrated and unless therapy is discontinued the climacteric indefinitely may be postponed."

It is well known that estrogen therapy frequently results in uterine bleeding. Although such an occurrence usually is due to overdosage, it is always alarming to the patient. If the bleeding is scant and of short duration, endometrial curettage may be deferred provided careful pelvic examination reveals no abnormalities. However, if there is any recurrence of bleeding, diagnostic curettage should be done immediately and the curettings examined by a competent pathologist to rule out carcinoma.

**INDICATIONS FOR ESTROGEN THERAPY**—Only a small percentage (10 to 20 per cent) of menopausal women require estrogen therapy. The outstanding indication is severe vasomotor symptoms (flushes, sweats, chills) that have not responded to general medical measures. It may be tried as a therapeutic test for relief of severe headache after careful examination has ruled out organic disease and other methods of treatment have failed. Such a trial may be of value also in some patients with painful joints (knees, shoulders). Its value in vaginitis secondary to atrophic changes in the mucosa is well recognized but in this instance local application is preferable. Many clinicians believe that hypertension which originates during the climacteric may be benefited by estrogen therapy. Its use is probably justified in the management of these cases but the administration, as already pointed out, may have harmful effects.

It is questionable whether estrogens should ever be given to relieve menopausal symptoms in patients who are experiencing the irregular uterine bleeding that is so common during this period. Such bleeding is most likely to occur during the early stages of ovarian failure and is often associated with excessive estrogen levels (polyfolliculin phase). If facilities are available, determination of the output of estrogenic hormones in the urine or a study of vaginal smears will settle this point. The first of these procedures requires a laboratory and special equipment to make hormone assays. The second has recently been simplified by Shorr who has developed a technic which can be acquired readily by one trained in routine clinical laboratory procedures. It is based upon Papanicolaou's studies which showed that the estrogen deficiency brings about "a vaginal smear pattern characterized by the absence of cornified epithelial cells, and the presence of many intermediate and small round and ovoid cells which originate from the deeper layers of epithelium plus many leukocytes." Variations in the smear pattern indicate various degrees of estrogenic deficiency. Although these studies are helpful in determining the need for estrogenic therapy, they are by no means essential for the intelligent clinical management of these patients. Careful evaluation of symptoms with special consideration of

the characteristic vasomotor disturbances usually provides a reliable therapeutic index.

**CONTRAINDICATIONS TO ESTROGEN THERAPY**—Estrogenic therapy should not be given in the presence of carcinoma or for relief of menopausal symptoms following surgical or radiation treatment of malignant disease. In no instance should it be initiated prior to a complete pelvic examination including diagnostic curettage and cervical biopsy when irregular bleeding or abnormal vaginal discharge is present. When given to control menopausal symptoms following radiation treatment of benign hemorrhage, it is likely to produce a recurrence of the bleeding. If symptoms attributed to the menopause are not relieved after a brief trial of estrogen therapy, it should be discontinued and the patient should be reexamined for evidence of organic disease.

**AVAILABLE ENDOCRINE PREPARATIONS—Estrogens**—For clinical use we have available the natural estrogens which are prepared from the urine of pregnant women and pregnant mares, and synthetic estrogens which are prepared in the laboratory and are chemically unlike the natural estrogens which are alcohols of the steroid group. The important natural estrogens are *estrone*, *estriol* and *estradiol*. The latter is the most potent and is often used in the form of the benzoate or the dipropionate. The estrone and estradiol preparations are the forms most commonly used for parenteral administration. The estrone sulfate is the most potent form for oral administration. The estriol preparations are much less potent. Estrone and its derivatives are usually assayed in international units while the estradiol preparations are assayed in rat units. The rat unit is three to five times as potent as the international unit. The present tendency to develop pure hormone products whose dosage can be expressed in weight gives promise of simplifying this problem for the practitioner.

The best known synthetic estrogens are stilbestrol and its more potent derivative, *diethylstilbestrol*. This compound is not related chemically to the natural estrogens. The dose is expressed in milligrams, one milligram being equivalent to approximately 25,000 international units of estrone. Its advantage lies in its low cost and in its effectiveness when given orally. Its chief disadvantage is the frequency with which it produces nausea, vomiting and headache. Novak reports that such symptoms occurred in 20 per cent of patients in his experience. The incidence of these symptoms can be reduced by using small doses, coating the tablets and limiting the treatment to short cycles.

**Androgens—Testosterone** and its esters are available. The dosage is expressed in milligrams and it is most effective when given intramuscularly although ethyl testosterone is potent when given by mouth. These preparations have been used in the treatment of menopausal symptoms because they are thought to depress the hyperactive anterior pituitary. They may be given in doses of 10 to 25 mg two or three times a week for a total of 250 mg. Because of the potential harmful effects and the uncertainty of its clinical effectiveness in the relief of menopausal symptoms the use of testosterone is not recommended.

**Thyroid**—Administration of thyroid substance is of value in the presence of hypothyroidism. The clinical features of the case are equally as valuable as the basal metabolic rate in deciding this point. When indicated it should be given in full dose over a long period with careful medical supervision.

**METHODS OF ADMINISTRATION AND DOSAGE IN ESTROGEN THERAPY**—Irregular and haphazard administration of estrogens should be avoided. Sporadic doses even though large can do little good and may 1

endocrine system in a state of imbalance. The best plan is to give the hormone for a short period of time, possibly for two or three weeks, and then stop for a week and repeat. These cycles of therapy should not be continued for more than two or three months and usually should be stopped much sooner. If severe symptoms recur the treatment may be repeated for one or two cycles. The objective should be to control the symptoms promptly, using large initial doses if necessary and then reducing the dose and the length of the cycles so that the smallest amount that will relieve the symptoms is given. Under no circumstances should the administration of estrogens be continued indefinitely.

Oral administration is highly satisfactory and is the method of choice in most patients. The initial dose should be small, 0.25 mg of diethylstilbestrol or 1 mg of estrone sulfate daily. This can be varied from time to time until the optimum dose is found. The untoward effects of oral therapy can be prevented in most instances by using small doses and shortening the period of administration.

Intramuscular injection should be limited to patients in whom relatively large doses are necessary to control severe symptoms quickly. Ten thousand international units of an estrone preparation or 2000 rat units of an estradiol preparation given every four days for three to six doses are usually sufficient. Occasionally larger initial doses are necessary but these should be discontinued as soon as possible in favor of oral therapy.

The vaginal administration in the form of suppositories is indicated when there is an associated senile vaginitis. Cyclic administration of 2000 international units every third day for six doses is usually sufficient.

The subcutaneous implantation of pellets or crystals of estrogenic substances has been used very satisfactorily. It may be of distinct value in occasional instances where administration of the hormone is needed over a long period of time. Such an instance may occur following surgical castration in a young woman.

**X-ray Therapy**—Attempts to depress the anterior pituitary have been reported with varying results. The danger of injury to the pituitary and adjacent tissues makes its use hazardous. It is not recommended.

#### BIBLIOGRAPHY

- Hamblen, E. D. *Endocrinology of Woman*. Springfield, Ill., Charles C Thomas, 1945.  
Hoffman, J. *Female Endocrinology*. Philadelphia, W. B. Saunders Co., 1944.  
Novak, E. *Gynecology and Female Endocrinology*. Boston, Little, Brown & Co., 1941.  
Papanicolaou, G. N. The Action of Ovarian Follicular Hormone in the Menopause as Indicated by Vaginal Smears. *Am J Obst. & Gynec.*, 31:806, 1936.  
Shorr, E. New Technique for Staining Vaginal Smears. *Science*, 91:579, 1940.

## THE TIMING OF OVULATION BY BASAL TEMPERATURE GRAPHS

PENDLETON TOMPKINS, M.D.\*

Two developments in the treatment of sterility are currently attracting attention. The first is the use of a precoital douche of Ringer's solution and glucose. MacLeod and Hotchkiss<sup>1</sup> found that by adding glucose to Ringer's solution the activity of sperm is prolonged. Reports on the use of this preparation, which is readily available,† are so encouraging that it should be employed often if not routinely. The patient is instructed to use the douche at the time when ovulation is anticipated and to try to retain as much of it as possible.

Some years ago it was hoped that electric methods would solve the problem of determining the time of ovulation. However, further experience with the potentiometer has thrown considerable doubt upon its reliability for this purpose. Even if it is reliable, the instrument is not generally available. Hence interest has grown in the use of graphs of the daily basal body temperature as an index to ovulation. This second important development in the study of infertility deserves full discussion.

Rhythmic variations in body temperature during the menstrual cycle were noted many years ago, were described in detail by van de Velde in 1904 and have subsequently been the subject of much comment. These fluctuations in temperature had no clinical significance until the mechanism of menstruation began to be understood. After it was known that ovulation occurs about fourteen days before menstruation it was apparent that the most striking changes in basal temperature also occurred at this time and a causal relation between the two phenomena was presumed.

Typical basal temperature graphs are shown in Figure 180, and the important characteristics are described in the accompanying legend. These three graphs are unusually fine examples of temperature curves. Such curves are not obtained unless the patient has been carefully instructed in the details of taking and recording her temperature. One can reduce the time necessary for proper instruction of the patient from fifteen or twenty minutes to five minutes by using a pair of forms prepared for the purpose. One sheet bears a detailed set of instructions and a sample of a properly executed graph, the other sheet is a blank grid devised to receive the temperature notations in graph

From the Department of Obstetrics, Graduate School of Medicine, University of Pennsylvania and the Philadelphia Lying in Hospital.

Associate in Obstetrics, Graduate School of Medicine, University of Pennsylvania, Philadelphia.

†Marketed as Nutri Sal by Ortho Pharmaceutical Corporation.

form Although these forms are available upon request\* they are not essential Physicians may draw their own forms upon ordinary graph paper Grids with five lines to the inch are most satisfactory, and if  $\frac{1}{6}$  inch is allowed horizontally for each day, and  $\frac{1}{6}$  inch vertically for each  $\frac{1}{6}$  degree Fahrenheit the resultant graph will be well proportioned The patient is instructed to take her temperature rectally with an ordinary clinical Fahrenheit thermometer for five minutes each morning upon awakening, before rising, drinking, eating or smoking Some investigators secure evening (bedtime) readings, and some have

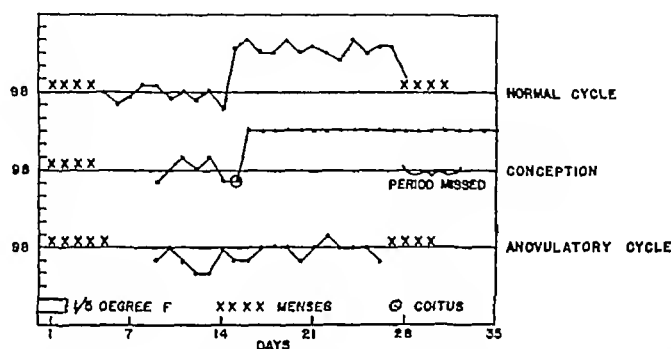


Fig 180—The first graph (*top*) shows the temperature curve during a normal menstrual cycle. During the first portion of the month the level is relatively low, it rises abruptly after a slight drop about fourteen days before menstruation and remains elevated until the next menstrual period. Then it drops and the entire cycle is repeated. The second graph was plotted by a patient with normal twenty-eight day cycles. On the fifteenth postmenstrual day her husband, who had been away at an Army Camp, came home "on a twenty-four hour pass." The following day the temperature rose, the patient conceived, and the high temperature level was maintained until after the period was due. If the high temperature level is maintained for more than sixteen days, in the absence of organic causes for fever, it is probable that the patient is pregnant. Hence the temperature graph is of some use in diagnosing pregnancy, and for this reason has been called "the poor man's Friedman test." The third graph was drawn by a woman of 43 whose menstrual intervals varied from month to month. Some cycles showed the typical curve of the first graph and it was assumed that ovulation had occurred. In the flat graph shown above it is presumed that ovulation did not occur. In this particular case the assumption was not confirmed by endometrial biopsy. This has been done in other cases.

the temperature taken orally or vaginally. After comparing various methods I believe that the most consistent and clear-cut graphs are obtained from morning rectal readings.

If the patient exercises reasonable care, few errors will arise. Since the desired information is obtained from temperature variations and not from absolute temperatures the accuracy of the thermometer is of no great importance. Precision in reading the thermometer is important. Patients are instructed to note on the chart any obvious cause

\* Address requests to Ortho Pharmaceutical Corp., Linden, New Jersey

for temperature variations such as respiratory infections. As a matter of fact, it is remarkable how severe infection of the nose and throat

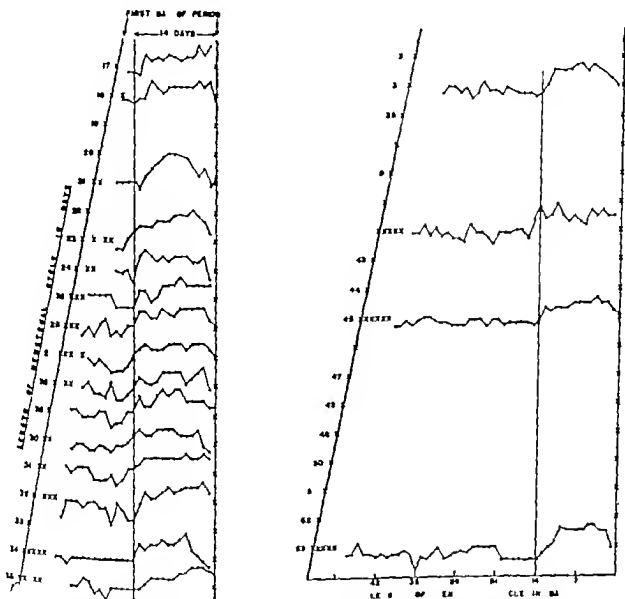


Fig 181.—This chart is composed of temperature graphs from many patients selected to illustrate the curves in cycles of different length. It will be noted that the change from the lower to the higher temperature level, or the "temperature shift," occurs in all cases approximately fourteen days before menstruation. It does not occur "midway between periods" except in those cycles which are about twenty-eight days in duration. In determining the point at which the temperature shift begins to become apparent one may make a reckoning not from the lowest point on the graph but from the average of all the temperatures which represent the low or preovulatory phase. For example, in the graph of the thirty-one day cycle the lowest temperature occurs seventeen days before menstruation, but the first distinct rise above the postmenstrual average temperature occurs on the thirteenth day before menstruation.

can be without producing a change in the basal temperature. On the contrary, a bottle of beer or two highballs the previous evening will often produce a rise of three- or four-fifths of a degree Fahrenheit.



Unexpectedly high or low readings are always suspect, and patients are instructed to shake down the thermometer and to repeat these readings before plotting them on the graph. An intrinsic error in the record arises through the fact that menstruation beginning after the patient has gone to sleep is usually not noted until the next day and hence may be recorded as beginning on the day after it actually commenced. Such an error adds one day to the apparent interval between the temperature shift and the next menstruation.

The critical reader may inquire whether there is any proof that the temperature shift is actually associated with ovulation. If he will for the moment regard the association as hypothetical, the graphs will be presented first and the question answered later.

The great body of evidence, derived from histologic examination of the endometrium and ovary, from hormone assays, from comparison with findings in the monkey, from searches for early human ova and from clinical experience point to the fact that, in the human, ovulation precedes menstruation by a fixed interval of about fourteen days. This belief is convincingly supported by Figure 181 which is made up of temperature graphs ranked according to the length of the menstrual cycle. It will be seen that the temperature shift always occurs in the neighborhood of fourteen days before menstruation, and that the interval between the temperature shift and the preceding menses varies in proportion to the total length of the menstrual cycle.

At this point a common mistake of clinicians may be pointed out. Since the normal cycle is twenty-eight days in length, and since ovulation occurs fourteen days before menstruation, it follows that in a twenty-eight day cycle ovulation occurs midway between periods. Misdirected by this fact, physicians often advise all their patients that ovulation takes place "midway between periods" and that intercourse at such a time is most likely to be fruitful. This is untrue, as reference to the graphs of the forty-five day cycle and the fifty-three day cycle in Figure 181 make quite clear. Patients should be told that ovulation occurs about fourteen days before menstruation and should be assisted in their efforts to calculate which day of the calendar month that will be.

If the patient has intercourse near the time of the temperature shift she will have a better chance of conception than if intercourse occurs only at other times in the cycle. The second graph in Figure 180 is an example of coitus accurately, though accidentally, synchronized with the temperature shift. Conception followed. Similar graphs are seen in Figure 183. Not only does intercourse at the time of the temperature shift offer the best chance of fertilization, but I have not yet seen a record followed by pregnancy unless intercourse took place at that time. Conversely, there are many records showing imperfect synchronization with no subsequent pregnancy, in these cases better timing was often successful.

The span during which the ovum is susceptible to fertilization is believed to be short, a matter of perhaps twelve or twenty-four hours. The capacity of the sperm for fertilization is likewise thought to be brief. Since the sum of the functioning lifetimes of the ovum and the sperm is short, and since it is only in this period that fertilization can

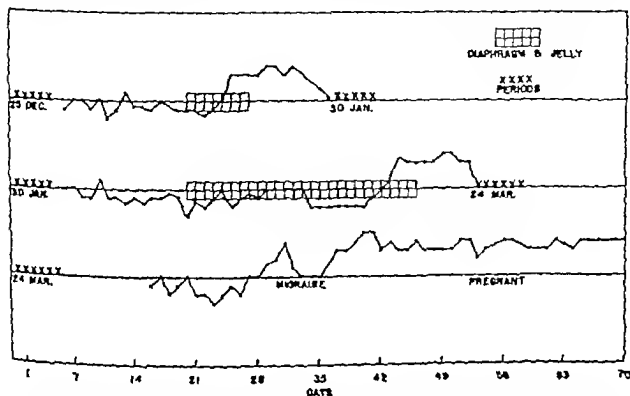


Fig. 182.—These graphs illustrate the use of temperature curves as an aid to birth control and also their use in planning conception. The patient has long cycles, and since she states that they are "never" less than thirty-five days in length, she was instructed to make use of her contraceptive diaphragm and jelly from the twentieth day of the cycle until the temperature shift had occurred and not to abandon use of the diaphragm and jelly until the high temperature level had been maintained for two days. In the December-January cycle the planned contraceptive measures (whenever intercourse occurred) during a period of seven days as shown. In the January-March cycle, which was fifty-three days in length, the plan required use of the diaphragm during a total period of twenty-six days as shown. No contraceptives were used during the first or last portions of either cycle since conception at such times would be most improbable if not impossible. After the March menstrual period the patient decided to conceive and abandoned all use of contraceptives. The temperature shift occurred about twenty-eight days after menstruation but the graph, unfortunately, is marred by fluctuations of temperature which may have been due to a four-day attack of migraine. However the high temperature level was maintained for about five weeks which justified a diagnosis of pregnancy subsequently confirmed.

occur, the importance of determining the time of ovulation is obvious if one is treating childless couples. Much has been made of the motility of the sperm and it is implied that motility is a gauge of the sperm's ability to fertilize the ovum. Possibly, this view is correct. However I cannot forbear saying that it seems to me as reasonable to estimate the fertility of pedestrians by viewing them from the height of the Empire State Building as it is to estimate the fertility of

spermatozoa by examining them under the ordinary microscope. In both cases one sees myriads of individuals agitated by an energy which appears purposeful. They move, to be sure, but of their age, their sex, their abilities we know little. In fairness to those who believe that motility is tantamount to potency, it must be admitted that bull semen

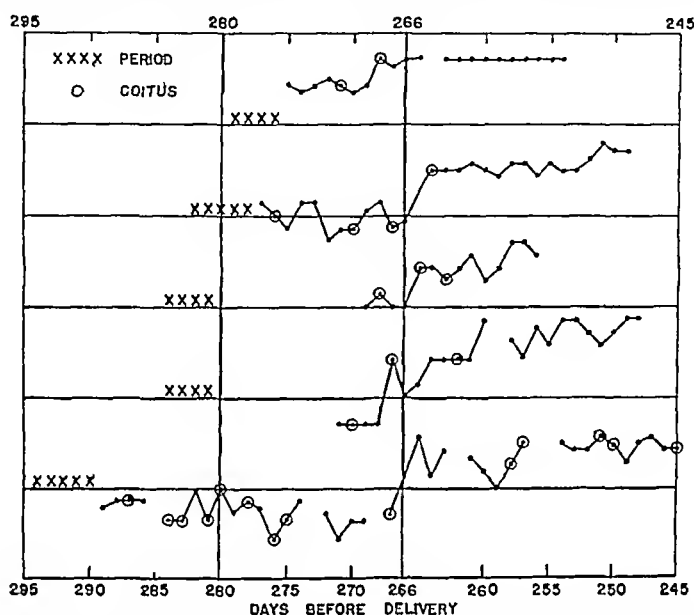


Fig 183—Since the interval from the last menstrual period before conception to delivery averages 280 days, and since the woman with regular twenty-eight day cycles ovulates about fourteen days after menstruation, it follows that the interval from ovulation to delivery, or the period of actual gestation, is theoretically 266 days. The chart above is composed of five graphs plotted by "sterility patients" in the course of routine studies. The graphs are aligned to show the actual number of days which intervened from the last menstrual period, and from the temperature shift, to delivery. In none of these cases was labor induced, none had twins, none had babies of less than  $5\frac{1}{2}$  pounds (2500 gm), none had cesarean sections. It will be seen that the interval from the first day of the menstrual period to delivery was 279, 282, 284, 284 and 294 days, and that the interval from the temperature shift to delivery was 268, 264, 265, 267 and 265 days respectively. It will also be noted that in each case coitus took place close to the time of the temperature shift. The chart may be regarded either as a demonstration of the fact that the temperature shift indicates ovulation, or, if that point be conceded, it may be regarded as confirming the theoretic duration of gestation, namely, 266 days.

is transported by veterinarians over great distances for the purpose of artificial insemination and that the same has been done with human sperm. It is said that in the case of the bat insemination occurs in the autumn and that the sperm survive until ovulation takes place the following spring. Leaving aside conjectural matters it can be said with assurance that, in the human, insemination close to the time of ovulation offers the optimum opportunity for fertilization.

It is apparent that if temperature graphs can be used to determine the time of maximum fertility they can also be used to determine the periods of minimum fertility. Details for this use of the graphs have been presented elsewhere.<sup>3</sup> One example is shown in Figure 182. It happens that this patient used a contraceptive diaphragm during part of each of the first two cycles. Abstinence during the same period would have been no less effective.

An interesting collateral study on temperature graphs is the estimation of the date of delivery from the date of the temperature shift

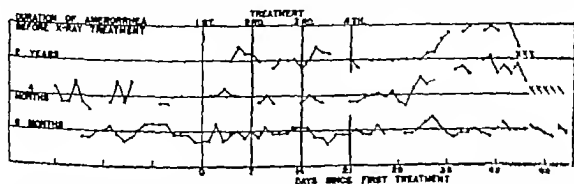


Fig 184.—The first graph (top) is from a patient whose last period before conception was dated September 1942. She was delivered in June, 1943 and did not menstruate thereafter. In September 1944 fifteen months after delivery, x-ray treatment was administered to provoke menstruation. A temperature shift developed and about two weeks later bleeding occurred. This was followed by regular cycles of five weeks' duration.

The second graph shows part of the record of a patient who menstruated at four to six month intervals. X ray was administered on May 1, 1944, four months after the last menstruation, in hope of improving the patient's chance of conception. On June 17 bleeding (menstruation?) occurred. This record is shown above; subsequent developments are presented in the last graph in Figure 185. About thirty days after the period of June 17 a temperature shift occurred and the patient conceived. She was delivered in April, 1945 (Details of this case have been presented elsewhere<sup>3</sup>).

tion, calculated by this graphic method, is so close to the theoretical 266 days And it is quite improbable that this degree of consistency between theory and observed fact would be maintained in a larger series of cases

Basal temperature graphs may also be used to evaluate treatment designed to produce ovulation Records of patients treated in collaboration with Dr Paul A Bishop, Director of the Department of Radiology of the Pennsylvania Hospital, are shown in Figure 184 These results were obtained by using the x-ray technic of Mazer, Baer and Greenberg <sup>4</sup>

It is now proper to tabulate the reasons for believing that the temperature shift in basal body temperature graphs is a phenomenon associated with ovulation

#### *Accepted Beliefs*

- 1 Ovulation occurs about 14 days before menstruation.
- 2 Conception is most likely to occur if intercourse takes place about the time of ovulation.
- 3 The average interval between ovulation and delivery is 266 days
- 4 X-ray treatment designed to stimulate menstruation must first produce ovulation

#### *Observations on Graphs*

- 1 The temperature shift occurs about 14 days before menstruation
- 2 Conception is shown to have occurred when intercourse took place about the time of the temperature shift, conversely, pregnancy has not followed when the interval between coitus and the temperature shift has exceeded forty-eight hours
- 3 The interval between the temperature shift and delivery averages 266 days in the five cases studied
- 4 X-ray treatment for amenorrhea was followed by a temperature shift and about fourteen days later by uterine bleeding

The reason for the temperature shift is not established Two suggestions have been made The first is that the temperature is elevated by progesterone during the latter portion of the cycle In support of this contention it has been shown that the temperature of postmenopausal patients may be elevated by administration of progestin The other suggestion is that during the preovulatory phase the temperature is depressed by estrogens This is said to be analogous to the depression of temperature when stilbestrol is administered during the puerperium Not only is the cause of the temperature shift undetermined, but the precise relation of the shift to ovulation is also unknown Examination of a large number of graphs will show that the shift occurs more often after than before the fourteenth premenstrual day Further, clinical experience shows that coitus shortly before the shift is often fruitful whereas intercourse at a later day in previous cycles has failed Since the temperature shift is probably a physiologic re-

sponse to some endocrine change it seems entirely probable that it would tend to lag somewhat behind the causative factor

It should be noted that while there are reasons for believing that the temperature shift follows ovulation, there is less reason for believing that ovulation, in the sense of expulsion of the ovum, has necessarily taken place because there has been a temperature shift. Experience will soon demonstrate that many women show a steplike rise in temperature (the thirty-one day cycle in Figure 181) during some cycles, while in other cycles the same patient will show an abrupt rise in temperature (the thirty-four day cycle in Figure 181). If intercourse is properly timed in all cycles it will be found that conception is more likely to occur when the temperature rise has been sharp. It therefore seems probable that there are differences in the character of ovulation as well as in the character of the temperature curve from month to month. Indeed, our knowledge of the inconsistency of physiologic reactions makes it seem entirely unlikely that ovulation would occur in precisely the same way during every cycle, or that conception could occur at every ovulation. At the present time Dr. Edmond J. Farris of the Wistar Institute of Anatomy in Philadelphia is carrying on a fascinating investigation which supports this idea. Since his work has not been published I cannot dwell upon it, but I may say that by means of biologic reactions he has been able to predict that conception would take place in certain cycles and that it would not take place in other cycles, and that these predictions could not have been successfully made from the temperature graphs or the records of coitus which his patients have kept.

#### SUMMARY

The chief uses of basal body temperature graphs as an index of ovulation are (1) as an aid in advising childless women of the time of maximum fertility, (2) as a means of planning conception during a certain cycle or season, (3) as a method of avoiding pregnancy useful to those who do not use contraceptives, (4) as a method for timing artificial insemination and endometrial biopsies, (5) as an aid in securing early human ova, (6) as a help in evaluating treatment designed to produce ovulation, (7) in occasional cases as a means of predicting the date of delivery.

#### REFERENCES

- 1 MacLeod, John and Hotchkiss, Robert S. The Use of a Precoital Douche in Cases of Infertility of Long Duration. *Am J Obst. & Gynec.*, 46:424-478 (Sept.) 1943
- 2 Tompkins, Pendleton. The Use of Basal Temperature Graphs in Determining the Date of Ovulation. *J.A.M.A.*, 124:698-700 (March 11) 1944
- 3 Tompkins, Pendleton. Basal Body Temperature Graphs as an Index to Ovulation. *J. Obst. & Gynaec. Brit. Emp.*, 52:241-252 (June) 1945. Report on the

same subject now in press Proc Conference on Sterility, National Committee on Maternal Health (1945)

- 4 Mazer, Charles and Baer, George Therapeutic Value of Low Dosage Irradiation of the Pituitary Gland and Ovaries in Functional Menstrual Disorders and Sterility Am J Obst. & Gynec, 37 1015-1024 (June) 1939

Mazer, Charles and Greenberg, Rose Low-dosage Irradiation in the Treatment of Amenorrhea Am J Obst. & Gynec., 46 648-652 (Nov) 1943

## TOXEMIAS OF PREGNANCY

MARIO A. CASTALLO, M.D., F.A.C.S.\*

THE etiological causes of the toxemias of pregnancy are not completely understood. The toxic effects of the pregnancy on the human structures, nevertheless, is well understood. The toxemias of pregnancy, from their earliest manifestations of nausea and vomiting to the last and dramatic stages of eclampsia, are thought by many to be one and the same process. The symptoms and signs differ only as to time of their occurrence, their severity and clinical manifestations.

Although there have been no startling new findings as to the causation of toxemia, nevertheless there have been some startling and definite advances made in its management and in its treatment.

Eastman and Wetheridge report that whereas the maternal mortality in toxemia of pregnancy was as high as 20 per cent, it is now down to 5 per cent. This low rate has resulted not because we know so much more about the disease but because the conservative treatment of eclampsia is started earlier and is more universal. Its fundamental principles are (1) elimination of the toxins by medical means, (2) the abolishment of drastic surgical procedures, and (3) early induction of labor if medical treatment of the patient does not show a decided improvement within a short length of time. These factors and better and earlier prenatal care have all contributed to the great saving of maternal lives in toxemia.

The greatest advances in the management of toxemia of pregnancy consist in the careful study of the blood pressure at frequent intervals, the assiduous regard for excessive gains in weight, constant watchfulness of the vascular tree by the use of the ophthalmoscope, and the institution of means to dehydrate the patient and keep her at rest. Better prenatal care and a keener regard for the clinical picture, together with the individualization of management and a realization by the medical profession that eclampsia and death are usually the result of neglect in the care of women who show changes in pregnancy which were thought unimportant, have been vital factors in the improvement in the mortality and morbidity statistics in toxemia.

Any classification of the toxemias of pregnancy must, because of the nature of the disease, be inadequate. The classification proposed by the American Committee on Maternal Welfare, although it does not cover completely all of the gradations of the toxemias, nevertheless does encompass the majority of them. The larger clinics and hos-

---

\*Associate Professor of Obstetrics, Jefferson Medical College. Chief Gynecologist to St. Mary's and St. Agnes Hospitals, Philadelphia.



pitals are using it for study and correlation of findings The classification is as follows

- |  |                                     |
|--|-------------------------------------|
| 1 Hypertensive disease                     | 4 Eclampsia                         |
| 2 Renal disease                            | 5 Vomiting of pregnancy             |
| 3 Preeclampsia, severe, preeclampsia, mild | 6 Acute yellow atrophy of the liver |
|  | 7 Unclassified                      |

To anyone who is interested in obstetrics it is immediately recognizable that a clear-cut distinction between these different conditions is often difficult There is overlapping between the various groups Rather mild types of eclampsia can easily pass into the severe type of preeclampsia, and the severe type of preeclampsia can and does develop into eclampsia

Confusion also occurs frequently in the differentiation of hypertensive disease, preeclampsia and the acute exacerbation of chronic conditions This differentiation cannot always be made unless the patient is followed not only through the course of pregnancy but also through the postpartum period and for a number of months or even years thereafter Nevertheless, we have in this classification a satisfactory working basis and its universal adoption for the classification of toxemias is urgently to be sought, in order that some standard may be used throughout the country

#### THE ETIOLOGY OF TOXEMIA OF PREGNANCY

It has been contended by many that placental infarctions are either the cause of toxemia of pregnancy, or they may be used as a diagnostic criterion of maternal toxemia Hill and Tremble in 1944 studied the placentas from 640 deliveries which were fixed in 10 per cent formaldehyde solutions for from four to six weeks, then examined closely for certain infarcts involving the placental villi Forty-two placentas from patients with a definite clinical picture of toxemia were examined but only eight of these had infarcts which were extensive enough to be distinguishable from the placentas of nontoxemic patients Thirteen of the 598 placentas from patients with normal pregnancies showed infarcts like the eight from the patients with toxemia Hill and Tremble were unable to satisfy themselves that the acute type of infarct described by Bartholomew and his co-workers was associated with toxemia

The theory that the posterior pituitary factor plays an important role in the toxemias of pregnancy was presented by Mukherjee in 1941 This investigator relied upon the anatomical observations of Cushing and Ahlstrom that there was morphological evidence of hyperactivation of the neurohypophysis in toxemias of pregnancy, and the biological researches of Anselmino and others pointedly suggested the possibility of such functional hyperactivity

Mukherjee conducted a series of experiments in fifty unselected cases of pregnancy toxemia—two of eclampsia, forty of preeclampsia, one of nephritic toxemia, three of accidental hemorrhage and four of hyperemesis gravidarum. He found that the blood in these patients revealed ultrafiltrates which showed melanophoric, antidiuretic and vasopressor properties. The author believes that the toxemias of pregnancy are intrinsically one disease with varied manifestations. In his experiments he found the type of the diuretic and vasopressor responses corresponded roughly with the predominant clinical manifestations of the patients from whom the ultrafiltrates were obtained. For example in all of the hypertensive cases, marked and moderate vasopressor responses were obtained. The only substance present in the human circulation known to produce this triple response is the posterior pituitary hormone. Mukherjee studied fifteen normal pregnant women and they gave very little or no response whatsoever to the ultrafiltrates or pitressin, while fifteen toxemic pregnant women responded to pitressin and to the ultrafiltrates similarly—that is, by significant increase in blood pressure and by oliguria. It thus appears that there is an increased concentration of the posterior pituitary hormone in the circulation of toxemic patients. This was corroborated by the biochemical investigation in which it was found that the rise of blood uric acid and the lowering of carbon dioxide combining powers of blood to the extent met with in toxemia of pregnancy could be produced experimentally by large and repeated doses of the posterior pituitary extract in normal women. These facts suggest that an increased concentration of the posterior pituitary autotoxin, or functional hyperactivation of the pars nervosa of the hypophysis, in all probability plays a considerable role in the etiology of toxemia of pregnancy.

Mukherjee states that the most common residual lesion in toxemia of pregnancy is essential hypertension and not chronic nephritis as was formerly believed. The persistence of hyperactivation of the posterior pituitary lobe and chronic vasospasms may satisfactorily account for the sequelae. What stimulates this hyperactivation is difficult to explain. The toxic manifestations produced experimentally in normal pregnant women required extremely massive doses of vasopressin. It was found that with only a small dose of this substance, or the ultrafiltrate, worse toxemic symptoms could be produced in persons already suffering from pregnancy toxemia. These observations, the author feels, show that toxemic patients are in some degree susceptible to extracts from the posterior pituitary lobe.

These theories of the etiology of toxemia of pregnancy, together with the many other experimentations which have been reported, remain inconclusive. The only known definite cause for toxemia of pregnancy is the pregnancy, whether in a patient who has or has not had preexisting disease.

#### SYPHILIS AND TOXEMIA OF PREGNANCY

In our clinic at the Jefferson Medical College Hospital which has been conducted exclusively for the treatment of syphilitic pregnant women since 1925 we have found no greater incidence of toxemia of pregnancy than we have in the prenatal clinic as a whole. These findings agree with those of Peckham who in 1941 concluded that antisyphilitic treatment administered to the pregnant syphilitic woman during pregnancy does not increase the incidence of toxemia of pregnancy. This author found that, in a series of 13,742 consecutive deliveries at the Johns Hopkins Hospital, the incidence of toxemia of pregnancy was somewhat lower in syphilitic than in nonsyphilitic patients. He could find no correlation between the stage of syphilis at the time of its diagnosis and treatment during pregnancy and the frequency of toxemia. The incidence of toxemia was low-

est in a group of syphilitic women treated before pregnancy, but not during, slightly higher in patients not treated, since he found the diagnosis of syphilis was actually higher in the group receiving treatment for toxemia during pregnancy.

Peckham thinks that these differences are all within the average of sampling error and the highest incidence in the treated group was well below that of the general clinic population. The amount of treatment employed was without significance. A number of patients had been treated in previous pregnancies without developing toxemia, and others were subsequently treated throughout one or more normal pregnancies. One-half of the treated patients evidenced toxemia before the first injection of an arsenical drug and no correlation was found between the development of physical signs and the specific number of injections previously given.

#### LABORATORY TESTS IN THE TOXEMIAS OF PREGNANCY

It is the consensus that the clinical findings are of much greater importance in the management of toxemia of pregnancy than the laboratory tests. Kriger and Rome, after a study of 652 patients, concluded that an evaluation of renal efficiency with the use of tests for albumin in the urine and urea in the blood did not give sufficient information. High blood urea values occur only when the kidney damage has become pronounced. They also found that the urea concentration excretion and the Fowweather clearance test offered a valuable means for detecting the intermediate as well as gross degrees of kidney damage and give information regarding improvement or deterioration of the kidney function.

Cuizza in 1941 discussed the various tests for functional activity of the liver and kidney and gave in detail the technic for determining Maillard's coefficient.

Cuizza's report is based on eight cases of hyperemesis gravidarum, twenty-six cases of albuminuria and nephropathy in pregnancy, and eight cases of eclampsia. In hyperemesis gravidarum he finds that the organ most seriously injured is the liver as shown by acetonuria, urobilinuria and a high Maillard coefficient, which is a true coefficient of acidosis. On the other hand, kidney function is almost normal as shown by absence of albumin in tests of the urine, normal azotemia and low blood pressure. However, he found that in the nephropathies of pregnancy, kidney function is much more seriously impaired than the function of the liver as shown by albumin, casts in the urine, high azotemia and high blood pressure.

In eclampsia, the function of both the liver and kidneys is seriously impaired. All of the functional tests show more or less deviation from normal. The type of liver injury in eclampsia is different from that in hyperemesis gravidarum, particularly in the absence of acetonuria. The mechanism of the acidosis shown by the high Maillard coefficient differs in the two diseases. In hyperemesis it is due to the accumulation in the blood of ketone bodies which are intermediate products of the abnormal metabolism of fat, while in eclampsia it is due to the accumulation in the blood of intermediate acid products of protein metabolism, among which Zweifel demonstrated sacrolactic acid which was derived from muscle albumins. He believes, therefore, that his study confirms the theory that eclampsia is not merely an aggravated condition of pregnancy nephropathy, but is an essentially different disease marked by pathologic conditions in the liver also. None of the tests used in determining liver and kidney functions is decisive in itself, but

taken in conjunction with the others, and with the clinical findings, it gives a criterion of the function of these organs

As to Maillard's coefficient, it was found to be of decided value in hyperemesis, in which condition it shows the condition of the liver function and the degree of acidosis. It is of value not only in diagnosis but in prognosis. It helps one to determine when therapeutic interruption of pregnancy becomes necessary. It is of less value in nephropathy and eclampsia, in which conditions the decision must be based on the clinical more than the laboratory data. In eclampsia immediate action based on the clinical picture alone is often necessary

Krieger and Norris concluded, after a study of 3000 tests for renal efficiency during and after toxemic pregnancy, that the blood urea test is useful in indicating gross renal damage resulting from severe toxemia of pregnancy, or milder toxemias in association with chronic nephritis during the pregnancy. The urea concentration excretion test is a much more sensitive test than the blood urea test and enables less gross renal damage to be detected during toxemic pregnancy. It can also be used in recovery of renal efficiency, or to prove the presence or absence of permanent damage by observation of the results of tests at certain intervals for some months after delivery

They also found that the presence of albumin in the urine of a large number of patients whose kidneys had recovered normal function in relation to the excretion of urea in tests two months after pregnancy, and the persistence of traces of albumin in the urine of many of these patients even twelve months after delivery, showed that this is an even more delicate means of indicating that a kidney is not completely normal. Renal function tests, they feel, are of great value in the treatment of recurrent toxemia and, if investigations are carried on over a period of months after the initial toxemia, they will give information useful in the management of subsequent pregnancies.

A study of the urea concentration-excretion tests during and after pregnancy shows that the excretion of urea by the kidney is decreased slightly even by normal pregnancy. The recovery of normal function takes place often within eight days, and usually within two months of delivery. Maximum urea excretion is obtained. Recovery from eclampsia is slower, the maximum excretory power being regained within twelve months.

The contention that renal insufficiency can be detected in a greater number of patients before delivery rather than during the puerperium was disproved. Renal function did not deteriorate in the interval beginning eight days after delivery and ending twelve months after delivery in two-thirds of the patients investigated, and it improved during this period in practically all the remaining patients. Deterioration in renal function two months after delivery was rare. It is the consensus that an increase in the blood uric acid content is the most constant finding in toxemia of pregnancy. The reason for this is easily understood when one realizes that the kidney is an organ which has a great deal of reserve and that its impairment must be almost com-

plete before signs of it are found in the blood stream. Laboratory tests alone are therefore no criteria for the institution of treatment.

### SYMPTOMS AND SIGNS

A number of symptoms and signs are more important in the diagnosis of toxemia than any of the laboratory studies, except perhaps the increase in blood uric acid.

Danger is imminent when a pregnant patient exhibits one or a combination of the following: (1) rising blood pressure, (2) increasing albuminuria, (3) rapid increase of weight, (4) diminished urine output, (5) increase in edema, (6) dimness of vision or amaurosis, (7) precordial pain, or girdle pain, (8) accelerated pulse, (9) increased depth of respiration, (10) torpor or excitability, (11) marked retinal edema.

### TREATMENT OF THE TOXEMIAS OF PREGNANCY

**Hypertensive Disease**—In the management of hypertensive disease complicating pregnancy, it is the consensus that any pregnancy superimposed upon hypertensive disease is prone to make the hypertensive disease worse. So-called essential hypertension, of which we know very little, is nevertheless a clinical entity. Whether the pregnancy should be allowed to continue in a patient with hypertensive disease will depend entirely upon the clinical findings and the evaluation of the patient as a whole. It is the feeling of most that a patient with essential hypertension should not become impregnated. Nevertheless, in our clinic and in others, many patients with essential hypertension have been carried through a pregnancy under a regimen of individualization. We have in many instances been able, as have others, to bring the patient at least to the point where she may have a viable baby before termination of the pregnancy.

**Renal Disease Complicating Pregnancy**—A patient with definite existing renal damage who becomes impregnated not only jeopardizes her own life but also the life of the child she is carrying. She definitely should avoid pregnancy. True renal disease complicating pregnancy is considered by many experienced practitioners to be an indication for the termination of pregnancy, nevertheless, the patient's wishes and her religious beliefs should be taken into consideration. The added stress and strain of an already overtaxed cardiovascular renal tree is often most injurious to the patient. The management should be individualized.

**Mild and Severe Preeclampsia**—In the management of mild preeclampsia, one must always bear in mind that the mild type of eclampsia may become a toxemia of pregnancy with complete eclampsia. One should consider every preeclamptic a potential eclamptic. At the slightest sign of deviation from the normal the patient should be treated immediately and adequately.

The indications for the institution of treatment in preeclampsia are (1) increase in blood pressure, (2) increase in weight out of proportion to the usual gain, (3) edema of the hands, face and ankles, and (4) albuminuria.

What is an abnormal rise in blood pressure? To give any particular numerical figure as the top level at which the blood pressure is to be considered dangerous is to our mind a fallacy. It is normal for a person's blood pressure during pregnancy to be lower than usual. A blood pressure of 100/60 may be the normal pregnancy blood pressure in a certain patient, and if this rises to 130/80 it is abnormal for her. She may be in just as much danger as the person who began her pregnancy with a blood pressure of 120/80 and sustained a rise to 140/90. Another most important consideration is that the diastolic blood pressure is the more important of the two. A constantly raised diastolic pressure is to be considered dangerous.

It is the consensus that 20 to 25 pounds increase in weight for the entire pregnancy is a normal gain, which amounts to approximately 2 pounds a month. If the patient gains a pound a week or more, she should be seen more frequently.

Swelling of the face, ankles and hands is an indication of faulty elimination and water retention. This also calls for watchfulness.

The appearance of albumin in the urine should be considered abnormal. A catheterized specimen is necessary for the test, inasmuch as a voided specimen from a woman, especially a pregnant woman, is not reliable because the vaginal secretions collected with it obscure the picture.

Upon the appearance of any of the above signs and symptoms during the course of pregnancy the following routine should be immediately adopted:

1. The patient should be advised to rest every afternoon for at least one to two hours.

2. Salt intake should be drastically curtailed, a salt substitute may be ordered, such as "Curtasal." The patient gets the taste of salt but curtails her sodium chloride intake.

3. Enough of a saline cathartic should be used to give the patient a watery bowel movement. Either epsom salts, one teaspoonful in the morning, or enough to give her one watery bowel movement a day, should be taken. Many patients are much more cooperative if they are asked to take citrate of magnesia. Citrate of magnesia may be kept cool in the ice box. A wineglass full or two in the morning before breakfast is usually sufficient to produce a copious watery bowel movement.

4. A high protein, low carbohydrate diet is also prescribed.

5. The patient is seen at more frequent intervals.

In many cases this regimen will bring the blood pressure down, reduce the gain in weight, relieve the swelling of the ankles, face and

hands and reduce the amount of albuminuria. If there is no response to treatment, or if during treatment the patient complains of blurred vision or headache, or continues to gain weight, and experiences girdle pains or pains in the epigastrium, she should be hospitalized immediately. Home care in these circumstances is permissible only when a competent nurse can be in attendance to maintain complete control over her treatment.

Once the patient is hospitalized she should be placed on a high protein, low carbohydrate diet in order that the excess protein which is being excreted in the urine may be replaced. An eyeground examination is done to obtain a clear picture of the vascular tree. Daily catheterized specimens of urine, complete blood count, estimation of the uric acid content of the blood, and a chart of the daily intake and output are obtained. The patient is given a sedative,  $\frac{1}{2}$  grain of phenobarbital three times a day is usually quite sufficient, or another sedative with similar action may be used. Complete bed rest is ordered, and the patient is placed between blankets so that she will sweat profusely. If the pathologic process is amenable to treatment, this regimen will ameliorate the symptoms present.

If after one or two days of this regimen the patient does not improve clinically, concentrated solutions of glucose are given intravenously. Two to five hundred cubic centimeters of 20 per cent glucose will usually stimulate the renal output. More highly concentrated solutions such as 50 per cent glucose used intravenously three or four times a day in conjunction with 2 to 5 cc of 25 per cent magnesium sulfate either intramuscularly, or given slowly intravenously, may be used to augment the above therapy in patients who do not respond. Plasma and whole blood are given intravenously only when indicated by the blood count reading and the blood protein globulin ratio. If the patient does not improve clinically under this regimen, then the toxemia is beyond medical care and the pregnancy should be terminated. The method of termination will depend entirely upon the parity of the patient and the type of cervix which is present. If the patient is a multipara and the cervix is soft, rupturing of the membranes under aseptic precautions after sensitizing the uterus by administering 2 ounces of castor oil the morning of the procedure will usually, after a short space of time, produce uterine contractions and institute labor.

During labor the patient should be given vitamin K for the protection of the premature child. Delivery is accomplished under some type of regional anesthesia, either local, spinal or caudal, and oxygen is administered to the mother during the time of delivery for the protection of the baby. When the cervix is completely dilated, outlet forceps, with episiotomy, are employed.

If the cervix is long and hard, especially if the patient is a primipara, induction of labor is not advised. The duration of labor may be long

and induction unsuccessful. In these instances a cesarean section is to be considered. A regional or a local type of anesthesia should be employed and no drug should be administered prior to the operative procedure which may narcotize the child. Oxygen is administered to the patient during the period of delivery as a protection to the child. Vitamin K is given to the child through its mother during the time that the patient is being prepared for the operative procedure and to the baby after its birth.

**Eclampsia.**—In the management of eclampsia the fundamental principles which were outlined above still obtain. Some patients will go into eclampsia no matter what therapy has been instituted to prevent it. Many are admitted to the hospital in eclampsia because of either inadequate treatment or lack of cooperation from the patient.

The most outstanding recent contribution in the therapeutic management of eclampsia is that of Rupert E. Arnell in January of 1945. Arnell reports a series of 142 consecutive cases of eclampsia without a maternal fatality. In the therapeutic regimen employed in this series nothing is either new or original, but details of treatment were carried out with meticulous care, to which is attributed the success which was achieved.

Arnell based his plan on ultraconservative concepts of management and the dangers of both overtreatment and indiscriminate treatment are evaluated. Constant observation of each eclamptic patient by an experienced staff throughout the entire course of treatment, which permitted careful integration of the various therapeutic components into an individualized regimen rather than application of a standardized routine of treatment, was the keynote of treatment.

Special factors of success also included frequent changes of posture, the use of oxygen therapy for respiratory stimulation during the acute stages of the disease, limitation of sedation to the dose necessary to control convulsions and hyperirritability, limitation of dextrose therapy to the smallest amount necessary to insure a satisfactory urinary output, with a return to oral fluids in a maximum amount, as soon as the swallowing reflex returned, delaying labor unless it occurred spontaneously, or until full recovery from the acute stages eventuated, induction of labor at the opportune time by the simplest possible method, medical induction being repeated if the first attempt was not successful, limitation of interference to an irreducible minimum, and the use of a local type anesthetic for all forms of operative work.

Arnell found that neither the future health nor subsequent pregnancies of patients were in any instance jeopardized by this plan of management. This statement is based upon observation of eighty-five patients at intervals of from five to fifteen weeks after delivery.

Adequate consideration of the baby yielded high dividends without increasing the maternal risk. The fetal mortality in this series was



24.2 per cent This showed marked improvement in the last two years, when the principles of consideration for the child were increasingly applied

Lack of adequate prophylaxis was the factor chiefly responsible for the resultant eclampsia in these 142 cases In this respect adequate care during gestation is not sufficient Intelligent care and judgment are needed during labor, at delivery, and throughout the puerperium

**Vomiting of Pregnancy.**—Vomiting of pregnancy may be either mild or severe Approximately 60 per cent of all patients have some gastrointestinal upset during the early months of their pregnancy Undoubtedly psychoneurologic tendencies are often a real factor in the aggravation of symptoms In any disease in which many therapeutic agents are proposed for the treatment, we may safely assume that none of them are completely successful

In the management of the early vomiting of pregnancy many agents have been used, among which may be mentioned injections of whole blood, vitamins, and the hormones The benefits from this therapy are debatable It probably is at least of some value psychologically. Personally I have discarded all types of injections except the injection of Vitamin B, for a period of five or six days The proper psychological approach during this early stage will in many instances prevent the development of pernicious nausea and vomiting The patient is made to realize that if she eats four times and vomits three times, one of the meals is retained, thus she is gaining and need not worry Too much concern by the family and especially the mother-in-law and the husband should be curtailed Small frequent meals, sedation and psychotherapy usually suffice

The slight nausea and vomiting of early pregnancy may develop into the pernicious type—an eventuality always to bear in mind If the patient's pulse rate starts to rise and her loss of weight is sufficient to cause alarm, she should be placed in a hospital immediately Here she should have complete rest, preferably in a private room or in a screened-off bed No visitors are allowed She is, in fact, completely segregated from the outside world

Our treatment consists, first, of a rectal suppository containing  $1\frac{1}{2}$  grains of phenobarbital, given every four hours We give the patient nothing by mouth Fluids and amino acids are administered intravenously We use subcutaneous solutions for the discomfort they produce and impress upon the patient that just as soon as she is able to take fluids by mouth these therapeutic agents will be stopped Vitamin B complex, 100 mg, is given by injection intramuscularly daily

Irving has described a plan of treatment which has proved very successful at the Boston Lying-In Hospital and which incorporates the fundamental principles to be utilized in these cases Under this regimen the incidence of therapeutic abortion has been reduced from 17.3 to 2.6 per cent and the mortality rate from 5.5 per cent to 0

The patient is isolated and receives sedatives. Intravenous infusions of glucose solutions are administered as described above. In addition, a Levine tube is passed and treatment carried out according to the following routine:

- Hours 0 Levine tube passed and the stomach gently washed with a small amount of warm water  
 Hours  $1\frac{1}{2}$  Murphy drip started 46 ounces of milk containing two heaping tea spoonfuls of Harris's yeast concentrate  
 Hours  $1\frac{3}{4}$  4 to 6 ounces of orange juice sweetened with corn syrup  
 Hours  $2\frac{1}{4}$  6 ounces of rich eggnog made with cream and egg  
 Hours  $3\frac{1}{2}$  Milk and Harris's yeast concentrate as above

This routine is repeated until fourteen out of the twenty-four hours are completed. Each feeding requires about forty minutes and is given at body temperature.

lutely negative, blood pressure will probably be normal or below normal and the characteristic eye changes of a cerebral tumor will likely be present X-ray study of the head will, in many instances, make the diagnosis clear

In *acute meningitis* the neurological signs are rather characteristic and these combined with a clinical history as well as a spinal puncture should promptly determine the true nature of this disease

*Eclampsia* is an extreme degree of preeclampsia in which the patient rapidly passes into deep drowsiness or coma The condition is often fatal and on postmortem examination the changes are characteristic of eclampsia

### CONCLUSIONS

The etiology of the toxemias of pregnancy is not clear Their management has been greatly improved, the mortality rate having dropped from 20 to 5 per cent in the past several years

The meticulous care of the pregnant woman with the added early treatment of the clinical signs has greatly increased the number of live births in the toxemias of pregnancy

Syphilis complicating pregnancy is not a great factor in the causation of toxemia of pregnancy

Laboratory tests, although of some value, have not proved of sufficient importance to warrant reliance on their findings in the management of toxemia of pregnancy Determinations of the blood uric acid and albumin of the urine are the most reliable laboratory tests when coupled with clinical findings

The management of hyperemesis gravidarum along more fundamental lines has reduced the mortality rate to zero and the incidence of therapeutic abortion from 17.3 to 2.6 per cent.

Arnell has shown that mortality in eclampsia can be reduced to zero, if meticulous care and individualization of treatment for each patient is assiduously adhered to

The modern management of the toxemic pregnant woman is based on early treatment and the induction of labor when medical treatment does not produce amelioration of signs and symptoms

### BIBLIOGRAPHY

- 1 Abhayaratne, O. E. R. The Public Health Aspects of Hypertensive Toxaemia of Pregnancy J. Ceylon Br., Brit. M. A., 40:94-103 (Sept.) 1943
- 2 Arnell, Rupert E. A Therapeutic Regimen for Eclampsia. Am. J. Obst. & Gynec., 49:49-80 (Jan.) 1945
- 3 Barnes, Josephine and Browne, F. J. Blood Pressure and the Incidence of Hypertension in Nulliparous and Parous Women in Relation to the Remote Prognosis of the Toxemias of Pregnancy J. Obst. & Gynaec. Brit. Emp., 52:1-12 (Feb.) 1945
- 4 Blazso, S. and Dubrausky, V. The Role of the Vasopressor and Antidiuretic Hormones of the Posterior Lobe of the Hypophysis in the Pathogenesis of the Late Toxemias of Pregnancy (Die Rolle des vasopressorischen und antidiuretischen Hormons des Hypophysenhinterlappens bei der Patho-

- genese der Spaetschwangerschaftstoxikosen) Arch f Gynaek., 170:651 1940
- 5 Bump W S. Management of Toxemia in the Last Trimester of Pregnancy Wisconsin M. J., 42 1037-43 (Oct.) 1943
  - 6 Chesley L. C. and Annitto L. C. A Study of Salt Restriction and of Fluid Intake in Prophylaxis Against Pre Eclampsia in Patients With Water Retention Am. J. Obst., 45:961 1943
  - 7 Colvin, E. D., Bartholomew R. A. and Grimes, W. H. A Comparison of Thyroid Extract and Iodine Therapy in the Prevention of Toxemia of Pregnancy Am. J. Obst. & Gynec., 43 183 1942
  - 8 Corr J E., Wagner W and Hetzer M. Intravenous Amino Acids in Nephrotic Toxemia of Pregnancy Am. J. Abst & Gynec., 47 70-80 (Jan.) 1944
  - 9 Cuizza, T. A Study of Hepatorenal Function in the Toxicoses of Pregnancy (Contributo allo studio della funzionalita epato-renale nelle tossicosi gravidiche) Ginecologia, Torino, 7:217 1941.
  10. Dexter L., Weiss, S., Haynes, F. W. and Sise, H. S. Hypertensive Toxemia of Pregnancy Pre-eclampsia and Eclampsia. J.A.M.A., 122 145 1943
  - 11 Dieckmann, W. J. The Treatment of the Patient With Toxemia of Pregnancy Proc. Amer. Coog. Obst. & Gynec., p. 235 1939
  12. Dieckmann, W. J. Hypertensive Toxemia of Pregnancy S. CLIN NORTH AMERICA, 23 11-20 (Feb.) 1943
  - 13 Duck, H. Hemotherapy in Pernicious Vomiting An brasil de gynec., 17 197-203 1944
  - 14 Eastman, N. J. and Whitridge, J., Jr. The Prevention of Toxemia of Pregnancy J.A.M.A., 120 729-32 (Nov. 7) 1942
  - 15 Gilbert, B. On Pregnancy, the Pregnancy Toxemias and Allied Conditions A Theory of the Origin of the Symptoms and Signs. Clin. Proc. (Cape Town) 3 1-54 (Jan.) 1944
  16. Hill, J. H. and Trimble, W. K. Placental Infarction as a Diagnostic Criterion of Maternal Toxemia. Am. J. Obst., 48:622, 1944
  - 17 Hofbauer, J.. New Orientation on the Etiology of the Toxemia of Pregnancy and Some Practical Applications. West. J. Surg., 49:615-18 (Nov.) 1941
  18. Huber Carl P. The Failure of the Conservative Treatment of Eclampsia Am J Obst. & Gynec., 49:81-84 (Jan.) 1945
  - 19 Hurst, Arthur Sir. The Hysterical Nature of the So-Called Pernicious Vomiting of Pregnancy Clin J., 72 169-172 (Sept.-Oct.) 1943
  20. Irving, F. C. The Treatment in Pernicious Vomiting of Pregnancy Virginia M. Monthly 67 717-24 (Dec.) 1940.
  - 21 Kapeller Adler R. The Significance of the Isolation of Histamine from the Urine in the Toxemia of Pregnancy J. Obst. & Gynaec. Brit. Emp., 48 155 1941
  22. Kapeller Adler R. The Histidine Metabolism in Normal and Toxaemic Pregnancy J. Obst. & Gynaec. Brit. Emp., 48 141 1941
  23. Krieger V. L. and Norris, N. Renal Function Tests in Normal and Toxaemic Pregnancy J. Obst. & Gynaec. Brit. Emp., 48 726, 1941
  24. Krieger V. L. and Rome, R. McK.. Toxaemic Pregnancy in Relation to Subsequent Pregnancies, with Special Reference to Renal Function Tests. M J Australia, 1:597 1941
  25. Kunz, Arturo Carlos. A New Treatment of Eclampsia (Un nuevo tratamiento de la eclampsia) Bol. de obst. y gynec. de Buenos Aires, 22 570-75 (Nov. 18) 1943
  26. Leary Deborah G. and Welt, L. G. The Antifibrinolysin Test in Normal and Toxemic Pregnancy Yale J. Biol. & Med., 16 193-96 (Dec.) 1943
  27. Mukherjee, C. The Posterior Pituitary Factor in Toxemias of Pregnancy J. Obst. & Gynaec. Brit. Emp., 48:586, 1941

- 28 Mussey, R. D and Hunt, A B The Toxemias of Pregnancy and The Management of Parturition J.A.M.A., 117 1309-13 (Oct. 18) 1941
- 29 Mussey, R. D., Hunt, A B and Sluder, F S Hypertension and Pregnancy Am J Obst., 45 224, 1943
- 30 Neuweiler, W and Stucki, A Polypeptides in the Serum During Normal Pregnancy, Labor, and the Toxicosis of Pregnancy (Ueber die Polypeptide in Serum bei der normalen Schwangerschaft, im Wochenbett und bei Gestosen) Klin Wchnschr., 2 1265, 1940
- 31 Nixon, W C W., Wright, M D and Fieller, E. C Vitamin B<sub>1</sub> in the Urine and Placenta in Toxaemia of Pregnancy Brit. M J, 1 604, 1942
- 32 Peckham, C H The Effect of Syphilis and Its Treatment on the Incidence of Toxemia of Pregnancy Am J Syph, Gonorr & Ven Dis., 25 280-85 (May) 1941
- 33 Piorli, G Daily Variations of the Blood Urea in Albuminurias of Pregnancy (L'oscillazione diurna dell' ureozotemia nelle albuminurie gravidiche) Atti d soc ital di ostet e gynec., 37 16, 1941
- 34 Ross, R. A Factors of Probable Significance in the Causation of the Late Toxemias of Pregnancy Proc Amer Cong Obst. & Gynec., p 320-25, 1939
- 35 Shute E. Hormone Management of the Nausea and Vomiting of Early Pregnancy Am J Obst. & Gynec., 42 490-92 (Sept.) 1941
- 36 Simrall, J O H An Analysis of Late Morbidity in 100 Cases of Pregnancy Toxemia. Am. J Obst., 43 858, 1942
- 37 Smith, E. N Nausea and Vomiting of Pregnancy Texas State J Med., 39 389-93 (Nov) 1943
- 38 Thierstein, S T The Management of Early Toxemias of Pregnancy J Kansas M Soc., 43 49-52 (Feb) 1942
- 39 Waters, E. G Weight Studies in Pregnancy Am J Obst., 43 826, 1942
- 40 Weinstein, B B, Wohl, Z., Mitchell, G J and Sustental, G F Oral Administration of Pyridoxine Hydrochloride in the Treatment of Nausea and Vomiting of Pregnancy Am J Obst. & Gynec., 47 389-94 (March) 1944
- 41 Williams, P F and Weiss, E. Application of the New Classification of Toxemias of Pregnancy in 318 Fatal Cases Am J Obst & Gynec., 45 1-14 (Jan.) 1943
- 42 Wilson, J St. G An Evaluation of the Treatment of Albuminuria of Pregnancy by the Water Balance Method, Assuming the Theory of Water Intoxication in Pregnancy I Obst & Gynaec Brit. Emp., 48 161, 1941

# THE MANAGEMENT OF THE PREGNANT CARDIAC PATIENT

CHARLES W SEMISCH, III, M.D \*

Few medical problems produce more diversification of general management than the patient with cardiac disease who becomes pregnant. The physician has not only clearly to evaluate the cardiac problem but must also consider the social, economic and religious factors. Any of the latter may alter sound medical judgment and lead to a doubtful procedure. The advice we must give to the patient who is childless may differ entirely from that which we give to a patient who already has one or more living children. One can readily see that each pregnant cardiac patient is a problem unto herself and decisions which hold for one will differ entirely for another.

In the past twenty years great stress has been laid upon the complications of pregnancy, particularly heart disease. Careful cooperation between the obstetrician and the cardiologist, together with the instigation of specified regular cardiac examinations, have negligibly lessened the maternal mortality.

The effects of pregnancy on the diseased heart must always be considered before pregnancy is advised. It is now well known that the work of the heart increases approximately 50 per cent during pregnancy and that this increase in work reaches its maximum at or about the eighth month. It is also known that the heart enlarges during pregnancy, that the blood volume increases, and that the minute output of blood increases as well as the velocity of the blood flow. The blood pressure generally falls during pregnancy, but may reach unexpected heights during labor. Since the basic principle of any cardiac problem is the reduction in the amount of heart work, it becomes necessary to appraise accurately each cardiac patient before or as soon after pregnancy occurs as is possible, and to separate those who can stand an increase in the cardiac load as contrasted to those who will probably have a break in compensation with the added burden of pregnancy. Of primary importance is the state of compensation of the circulation. If there has been previous decompensation or if the patient has evidence of heart failure when first seen, it is best to advise that pregnancy should not be contemplated or no further pregnancies undertaken.

## PREGNANCY IN THE PRESENCE OF VARIOUS CARDIAC CONDITIONS

There are two general groups of cardiac patients who, we may assume, have a normal heart. I refer to those who have one of the types

Associate Cardiologist, Jefferson Medical College Hospital, Philadelphia.

of functional heart disease and those who have systolic mitral murmurs, either of doubtful or specific origin. Of the remaining cardiac patients subject to pregnancy, 90 per cent will have rheumatic valvular heart disease. The remaining ones will be divided among the hypertensive, congenital, syphilitic and coronary groups. Let us first consider the miscellaneous groups.

**Hypertensive Disease.**—In general, patients with an elevation of systolic and diastolic blood pressure do not tolerate pregnancy well. On occasions, the tremendous desire of the patient to have a child, or the religious aspects will alter our judgment and we may permit individuals who do not have a marked elevation of blood pressure (above 160–180/90–100) and, who do not have significant kidney and eye-ground changes, or a history of previous decompensation to go through one pregnancy. However, it is a known fact that following the pregnancy hypertension usually increases and the life expectancy of the individual is shortened.

**Congenital Heart Disease.**—This group is divided into two principal classes, namely the cyanotic and acyanotic groups. The cyanotic group should never become pregnant and if they do, therapeutic interruption is mandatory. The acyanotic group (provided there has been no history of previous decompensation) can generally tolerate pregnancy fairly well and subsequent pregnancies will depend on whether the patient developed heart failure and whether there was an increase in the degree of cardiac damage. I have personally observed a woman who has had a patent ductus arteriosus go through four pregnancies without a mishap.

**Syphilitic Heart Disease.**—Since vascular syphilis has a predilection for the aortic valve, luetic heart disease if complicated by pregnancy has potential aortic valvular disease as the main factor. These patients usually tolerate pregnancy well, provided that the aortic insufficiency is an early lesion. If aortic insufficiency can be clearly demonstrated and there is no history of a previous break in compensation, one pregnancy may be permitted—other factors excluded. A history of previous decompensation is an indication for the interruption of the pregnancy. Aneurysm is a definite contraindication to pregnancy and therapeutic interference should be done at once.

**Coronary Disease.**—Coronary disease in my opinion is a definite contraindication to pregnancy, and early therapeutic abortion must be strongly urged.

**Cor Pulmonale.**—It has been shown that pregnancy does not interfere with the vital capacity in the later months of pregnancy, and since the burden of the work would have to be done by the left ventricle, it will not harm a patient with longstanding pulmonary disease and right-sided enlargement to go through pregnancy. In fact, our experiences have shown that pregnant patients are quite comfortable during the latter months of their pregnancy.

**Rheumatic Heart Disease**—Most of the patients with rheumatic heart disease who become pregnant will have mitral insufficiency, characterized by a rough-blowing systolic apical murmur, usually of a grade 2 or 2 plus or more. If there is no history of previous decompensation, these patients tolerate pregnancy well and can be considered as normal subjects. A small percentage will subsequently develop heart failure. Our main problem is with women who have mitral stenosis or aortic disease or both. Here again, the history of previous decompensation, the size of the heart, the electrocardiographic evidence of no to marked myocardial impairment must influence one's decisions, for a previous history of failure or marked cardiac enlargement is a definite contraindication to pregnancy. The patient with acute rheumatic fever or auricular fibrillation should not contemplate pregnancy. Auricular fibrillation that develops during early pregnancy is likewise an indication for therapeutic interruption. It is generally agreed that abortion in the early months of pregnancy does not preclude the same dangers that it does in the later months. It is therefore important that our decisions be made early, for the procedure is comparatively harmless during the first three months. It has been our policy to permit patients with mitral stenosis with no decompensation or history of failure to go through one pregnancy. Subacute bacterial endocarditis definitely is a contraindication to pregnancy.

The concepts noted above are, of course, generalities and there are many other personal, social, economic and religious factors which will alter one's sound judgment. When possible, even when the exact state of the heart is in doubt, the wish of the patient may warrant a slight added risk, for the joy of having a child is a great contrast to a childless life.

#### THE GENERAL MANAGEMENT OF THE PREGNANT CARDIAC PATIENT

There are three periods in the course of pregnancy during which decompensation is most apt to occur. It may first be detected about the fourth to the fifth month, or at the time that corresponds to the formation of the placenta, which functions as an arteriovenous anastomosis. It is at this time that the first appreciable increase in cardiac work occurs. Between the seventh and eighth month is the second period during which heart failure is most apt to occur, or at the time at which the cardiac load has reached its peak. The third period in which a break in compensation may occur is during labor itself. This produces a sudden tremendous load upon the myocardium and breaks in compensation that occur are apt to be sudden and of the left ventricular type.

The cardiologist's part *in pregnancy* is two-fold (1) he must appraise any existing cardiac lesion and the state of the myocardium (2) if it is damaged, he must attempt to lessen the amount of cardiac



work by careful instruction and guidance. It has been my policy to place all pregnant cardiac patients routinely on the following regimen:

- 1 A low caloric diet, poor in salt and high in vitamins, is advised. The patient is cautioned not to exceed the usual gain of 20 pounds during pregnancy. Salt and water retention and an increase in weight are definite burdens on the myocardium.
- 2 Proteins are given freely, since hypoproteinemia and resulting edema can also produce an increase in the myocardial load.
- 3 Ferrous sulfate is given in a dosage of 6 grains three times a day to combat or prevent the anemia of pregnancy, for it is well known that a diminution in the number of red cells produces an increase in cardiac effort.
- 4 Tight supports are prohibited.
- 5 Activities are restricted and specified rest periods are strongly advised.

When heart failure occurs in patients with heart disease, it is usually manifested by increasing dyspnea, cough, swollen ankles, and basal rales. If failure occurs early in pregnancy and is severe, interruption of the pregnancy is strongly advised. If it occurs during the second trimester our decision is more difficult. One must consider the degree of failure and the viability of the child. It may be necessary to perform an abortion at the fourth, fifth or sixth month. Sometimes the outlook will not be favorable regardless of the course pursued. When failure is detected, these patients are placed upon the following regimen:

- 1 Bed rest (absolute and complete) is ordered.
- 2 The general measures mentioned previously must be adhered to rigidly. If the symptoms of failure do not subside in four or five days, digitalis must be given. If the failure is severe, the more rapid methods of digitalization are indicated. It is my practice to give 0.5 to 1 *cat* unit of digitalis per day throughout the remainder of her pregnancy.

It should be borne in mind that maintenance doses of digitalis must be adequate and that this is truly an individual issue. There are some who believe that digitalis need not be given, but I personally feel that it is more beneficial than harmful.

Women who have had decompensation during the first and second trimester are placed on almost absolute bed rest during the last few months. Arrhythmias that may develop after the fourth or fifth month, namely, paroxysmal tachycardia, auricular fibrillation, or frequent extrasystoles can usually be successfully managed by the use of small doses of quinidine. Calcium gluconate intravenously may control severe paroxysms. Persistent arrhythmias, I believe, are definite indications for therapeutic interruptions regardless of the period of gesta-

tion. Patients who present failure in the last trimester are best delivered by elective caesarean section

Heart failure *during labor* is usually of a sudden precipitous nature and is manifested by sudden pulmonary edema, cyanosis and hemoptysis (acute left ventricular failure). This is best managed by morphine, oxygen, phlebotomy and, if no digitalis has been taken during the previous three weeks, ouabain, 0.5 mg intravenously, is given. This is followed in two or three hours by one large dose of digitalis parenterally, usually 3 to 5 cat units. Two or 3 cat units by mouth every six hours for two to three days may then be given. Sudden breaks in compensation during the puerperium are usually of the same variety as just mentioned and are treated in the same manner.

The *choice of an anesthetic*, if needed, is largely an obstetrical problem. In general, cardiac patients do well with ether. Recently, caudal anesthesia has proved very satisfactory. It has been our custom in patients who present decompensation at or near term to do a caesarean section under local anesthesia, particularly in the primiparous patient. Caudal anesthesia has also been beneficial in delivery by the vaginal route since it reduces the added stress of labor to an almost negligible factor.

In severe cardiac patients, the problem of *sterilization* almost always arises and I should like to state definitely that caesarean section should never be done with the purpose of ligating the tubes at the time of operation. One has no assurance that the child will survive delivery or even the first year of life. One may find later that the first pregnancy was tolerated quite well and a second child may be desired. If the first attempt to have a child is uncomplicated, it is strongly advised that the patient become pregnant as soon as possible since the added load is borne far better in the early years than later. Furthermore, the mother will have a longer period in which to enjoy her children. Sterilization should be advised only when it is certain that under no circumstance will the mother be allowed to go through further pregnancies.

It is always well to keep in mind that every cardiac patient is an individual problem and that when pregnancy occurs the problem is even more personal. Therapy and procedure for one individual with a given lesion will differ entirely from that of another similar individual. In general, if one must err, it is far better to err on the safe side. However, in conclusion, it must be always remembered that there is no other problem in medicine in which the patient's wish and desire must be so strongly heeded, in which sound clinical judgment is so often willfully ignored.

## PREGNANCY AND TUBERCULOSIS

DAVID A. COOPER, M.D., F.A.C.P.\*

### INFLUENCE OF PREGNANCY ON TUBERCULOSIS

THE influence of pregnancy on tuberculosis is a complex problem and one that has been discussed pro and con for many years. It is still far from being entirely settled. That this state of affairs persists is understandable, if we appreciate the varied manifestations and reactions of the individual to tuberculosis, and add to this the variable reaction of the individual woman to pregnancy. Krause,<sup>1</sup> in an editorial on the subject a few years ago, summed up the problem with this question, "May it not be that pregnancy exerts a harmful effect on tuberculosis in those women who, without tuberculosis, would naturally tolerate pregnancy poorly, and a harmless, or even beneficial effect on those women, who, without tuberculosis, would stand pregnancy well, or even have their bodily economy improved by pregnancy?"

The literature on the subject is extensive and, in the earlier writings, pregnancy was recommended as a therapeutic measure for tuberculous girls. Later, we find that the pendulum had swung to the opposite extreme, as is so often the case in medical thinking, to such an extent that abortion was advised in every pregnancy occurring in a tuberculous patient. In recent years, this point of view has been modified and there is considerable evidence to justify it. However, as late as 1936, DeLee<sup>2</sup> stated that until it can be incontestably proved that pregnancy actually improves the tuberculosis, the course of early interruption in every case of active tuberculosis is most charitable.

What, then, are the basic facts in this problem? The first is the difference in the tuberculosis mortality curve in females during the childbearing period, when compared to the male mortality curve of the same age group. In the two sexes the death rate runs parallel until the age 15, when there is a sharp rise in the female mortality curve, with a high plateau, until age 35, when there is a rather abrupt drop, whereas, in the male, there is a gradual rise, which continues well past this age. This fact in itself suggests a definite relationship between childbearing and tuberculosis incidence and mortality. In the city of Philadelphia, 20 per cent of deaths among women in the childbearing

---

From the Department of Medicine, School of Medicine, University of Pennsylvania, Philadelphia

\* Associate Professor of Medicine, Graduate School of Medicine, and Assistant Professor of Medicine, School of Medicine, University of Pennsylvania, Physician, Pennsylvania and Philadelphia General Hospitals, Assistant Physician, University of Pennsylvania Hospital



Within the past few decades, a number of *experimental studies* have been carried out in an attempt to solve the problem of the influence of pregnancy on tuberculosis. In 1916, Norris<sup>8</sup> stated that pregnancy definitely shortens the life span of tuberculous guinea pigs, and in 1917 Theobald Smith<sup>9</sup> stated that, in cattle, parturition is frequently followed by generalization of a local tuberculosis, with speedy decline and death. Mueller,<sup>10</sup> in 1923, concluded that pregnancy has a favorable influence on the course of tuberculosis in guinea pigs. Burke<sup>11</sup> in 1940 and Wade<sup>12</sup> in 1942, studying the influence of pregnancy on experimental tuberculosis in rabbits, concluded that the course of tuberculosis was not appreciably influenced by pregnancy. Within the past few years a number of studies have been carried out on the influence of various hormones on experimental tuberculosis in animals. In 1937, Steinbach and Klein<sup>13</sup> reported that antuitrin-S exerts a beneficial influence on experimental tuberculosis. Brack and Gray<sup>14</sup> were unable to detect any effect on resistance to tuberculosis in animals, kept in a high state of hyperestrinism. Long and Vogt<sup>15</sup> found no significant effect of gonadotropic hormones upon tuberculosis in mice. Carnes and Biskand<sup>16</sup> obtained no appreciable effect from treating tuberculous animals with testosterone propionate. Green and Morgan<sup>17</sup> obtained no effect from injections of progesterone in tuberculous male guinea pigs. Lurie,<sup>18</sup> in a recent unpublished study, using inbred rabbits of low, genetic resistance to tuberculosis found that estrogen uniformly retards the progress of the disease at the site of inoculation, in the draining lymph nodes and in the internal organs. That the rabbits injected with estradiol were actually under the physiologic influence of estrogen was demonstrated by the fact that the uterus of the estrogen-treated rabbits weighed much more than the uterus of the corresponding litter mates, which had not received the hormones. He concludes, therefore, that estrogen increases resistance to tuberculosis.

In similar experiments performed on highly inbred rabbits of high genetic resistance to tuberculosis, with the purpose of determining the effect of corpus luteum hormone on the progress of the disease, the following observations were made. To obtain a continuous, natural corpus luteum effect, experimental animals received from 0.02 to 0.1 mg of chorionic gonadotropin intravenously every tenth day, and a control group received none. It was found that, in the majority of instances, the presence of corpus luteum or corpus lutea cells in the ovaries was associated with an enhancement of the tuberculosis at the site of the inoculation and in the internal organs, as compared with the untreated controls. Furthermore, the number of organs to which the disease has spread was markedly increased in the rabbits treated with the hormones as compared with the controls. It is noteworthy that the intensity of development of tuberculin sensitivity was conspicuously retarded in the animals under the influence of corpus luteum hormone, since it has been shown previously that, in rabbits of low genetic resistance to the disease, the development of tuberculin sensitivity in response to heat-killed tubercle bacilli is markedly slower than in animals of high genetic resistance. It is clear that the presence of corpora lutea in the ovary is associated, not only with an enhancement of the tuberculous process and acceleration of dissemination of the disease, but also with a fundamental alteration in the response of the animals to the infection in the direction of increasing susceptibility. If these hormones exercise similar effects in the human being, one may expect that, during the estrogen phase of the menstrual cycle, the progress of tuberculosis should be retarded, whereas, during the corpus luteum phase of the cycle, dissemination of the disease would tend to be accelerated. Likewise, in the first month of pregnancy, when the corpora lutea are most active, the disease would tend to spread.

These experimental studies tend to confirm the clinical impression that has developed from observing the influence of pregnancy on

tuberculosis They also give a clue to some of the confusing factors that play a part in tuberculosis complicated by pregnancy That other factors are present there seems little doubt Pregnancy, in itself, induces physical and mental stress and strain and, if our present concept of the treatment of tuberculosis is correct, these additional factors of stress and strain predispose to the activation or reactivation of a latent or healed tuberculosis

It is generally accepted that a nutritional factor is associated with resistance to tuberculosis Nausea and vomiting in the early months of pregnancy may be severe enough to interfere with normal nutrition and thus could be a factor in the reactivation of a latent tuberculosis In my own experience clinical evidence tends to support this theory Nausea and vomiting not only affect nutrition but cause loss of sleep and rest, thus contributing additionally to the reactivation of a latent tuberculosis

That the rising diaphragm, during the latter months of pregnancy, has a beneficial influence on the course of the tuberculosis is borne out by clinical experience, as is the claim that its sudden descent, following delivery, has a deleterious effect.

Various *chemical changes in the blood* during pregnancy have been mentioned as having an untoward influence on the course of the tuberculosis. The most notable among these is blood calcium but at the present time there is no valid proof that a calcium deficiency contributes to the lowering of resistance to the tubercle bacillus. The high blood cholesterol associated with pregnancy has been suggested as a factor but in other conditions in which hypercholesterinemia is present, there is no demonstrable increase in susceptibility The view has been expressed that the loss of fluid such as blood and milk, during and after delivery, explains the increase in tuberculous activity which may occur at that time. Tuberculin energy which is said to occur in pregnancy has been suggested as a factor in the reactivation or progression of tuberculosis this evidence, however is rather inconclusive The long muscular strain, loss of blood and exhaustion associated with a long labor may well be a factor in the reactivation of a latent tuberculosis. Jamison<sup>19</sup> has suggested that increase in the capillary permeability associated with pregnancy might have a possible deleterious effect upon the tuberculous woman. The capillary permeability increases up to about the seventh month of pregnancy and then decreases toward the end of gestation, only to undergo a sudden rise that attains its highest point on the third and fourth day postpartum. It has been suggested that the proteolytic ferment concerned with the involution of the uterus may act in the same way and cause a reactivation of a tuberculosis, with softening of the focus.

In view of all of these factors that might influence tuberculosis in the pregnant woman, it is surprising to find that adequately treated tuberculosis withstands pregnancy well. Ornsteen and Covnat,<sup>20</sup> reporting on the influence of pregnancy on pulmonary tuberculosis, report a group in which eighty-five tuberculous pregnant patients were studied Of these, thirty-one (36 per cent) died, in fifteen (18 per cent) the tuberculous process was unimproved or progressed, and in thirty-nine (46 per cent) it improved In other words,

54 per cent of their patients died or did poorly. These findings alone seemed to indicate that pregnancy has a deleterious effect on tuberculosis, but in comparing these statistics with those of a group of female patients with tuberculosis uncomplicated by pregnancy they found that in the latter group 33 per cent died, 31 per cent were unimproved and 36 per cent were improved. They concluded therefore that the pregnant woman with tuberculosis stands as good a chance as her nonpregnant sister. They went further and classified the group of cases, not only as to the extent of disease, but also as to type of disease and concluded as follows, "All our deaths in the pregnant series at the Seaview Hospital were in the caseous-pneumonic group. On the other hand, in the resolving, exudative and chronic productive group, in which the prognosis is better and usually good, there were no deaths in the hospital in thirty-four such cases, and all of these patients were discharged improved. Pregnancy had only a minor effect on the prognosis of the disease in the caseous-pneumonic group, for which it shortened the usual span of life, compared with the nonpregnant group." In a subsequent study of eighty-two pregnant, tuberculous women by Ornsteen and Epstein,<sup>21</sup> there were fifty-nine cases of caseous-pneumonic tuberculosis, eight cases of resolving, exudative tuberculosis, and fifteen cases of chronic, productive tuberculosis. There were ten deaths, all of which were in the cavity type of disease. Collapse therapy was done in forty-seven out of forty-nine cavity cases. In twenty cases in which the cavity was closed with pneumothorax therapy the women were discharged from the hospital with negative sputum. Among thirteen women in whom the cavity was not collapsed by pneumothorax, nine died, in one the tuberculous process progressed and in three it was unchanged. In fourteen cases in which thoracoplasty was done, thirteen patients were discharged with arrested cases of pulmonary tuberculosis and one case was unchanged. In the remaining twelve cases, no surgical treatment was used and one patient died, in five the condition was unchanged and in six it was improved. In the eight cases of resolving, exudative tuberculosis, all of the women were discharged with negative sputum. In the fifteen cases of chronic, productive tuberculosis, all patients were discharged with negative sputum. On the basis of the above, Ornsteen and Covnat conclude that pregnancy has no influence on the course of pulmonary tuberculosis, and that the prognosis depends upon the character and control of the pulmonary tuberculosis, not upon the complicating pregnancy. The death rate among eighty-two tuberculous, pregnant women was reduced, with the aid of collapse therapy, to 12.2 per cent.

Mariette, Lawson and Litzenberg,<sup>22</sup> reviewing twenty years' experience in the management of pregnant tuberculous women at the Glen Lakes Sanatorium, in which they have had ninety-six full term pregnancies in eighty-six tuberculous women, with a mortality rate of 18.3 per cent, which compares favorably with a mortality rate of

39 per cent in nonpregnant tuberculous women in the age group 18 to 39 years, concluded that treatment of the pregnant woman with tuberculosis by modern methods of combating the disease, together with good prenatal care, apparently offers her as good a chance of recovery from her tuberculosis as though pregnancy did not exist.

#### MANAGEMENT OF THE PREGNANT TUBERCULOUS WOMAN

Before going into the details of management of recognized tuberculosis complicated by pregnancy, the importance of unrecognized tuberculosis should be stressed. It is in this group that so many of the pathetic cases fall, in which a pregnancy is followed by a rapidly progressive and fatal tuberculosis. An appreciation of the high incidence and mortality of tuberculosis during the childbearing age should make the obstetrician tuberculosis conscious. The following case is a good example of the dire results of unrecognized and untreated tuberculosis, associated with pregnancy.

The patient was white and gave a history of having had a "spot on her lung" at 19 years of age, which was said to have healed. She was married six years later and two years thereafter became pregnant. She went through her pregnancy normally except that she felt that it took a great deal out of her. Following delivery she failed to regain her strength and continued to lose weight and had an afternoon fever with cough and sputum. A chest x ray at that time showed extensive tuberculosis of an acute, exudative type and shortly thereafter she developed a hemogenous dissemination and died.

Had this situation been appreciated early during the pregnancy, the end results might have been prevented. Most experienced obstetricians have observed this same sequence of events, and that is why so many obstetricians favor interruption of pregnancy when associated with tuberculosis.

At this time, when so much is written about the prenatal care of patients, the importance of some form of roentgen examination of the chest as a method of finding tuberculosis cannot be too strongly stressed. A roentgen examination of the chest of the pregnant woman is just as important as the routine Wassermann test and, with the modern methods of examination, just as simple and economical. The physical examination alone is no longer considered adequate to rule out the presence of significant pulmonary tuberculosis. The 14 by 17 inch celluloid film is undoubtedly the best, but also the most expensive, method of chest roentgenography. Any of the accepted miniature film photofluorographic methods are quite satisfactory and quite economical. The fluoroscope also is of value, but it has a number of disadvantages, namely, visual limitation, the personal equation and the lack of a permanent record. When a routine roentgen examination of the chest becomes a part of a prenatal examination, we will have gone a long way toward controlling the problem of tuberculosis and pregnancy, because it has been well shown and is generally accepted that



a patient with recognized tuberculosis, if the disease is rigidly treated tolerates pregnancy well

The management of tuberculosis complicated by pregnancy dependent upon a number of factors. The first is the extent and type of disease. A woman with known tuberculosis, whose disease has been arrested for a period of from three to five years and is not too extensive, can usually stand pregnancy without difficulty. She should, however, be under medical supervision during the entire course of pregnancy and for at least a year thereafter, and her disease should be followed by serial chest roentgenograms. For those who develop tuberculosis early in their pregnancy, the question always comes up to whether or not pregnancy should be interrupted. At the present time a hard and fast rule should not be made. The general trend is certainly away from abortion, and it should be brought out that therapeutic termination of a pregnancy in a tuberculous woman is without danger. All of the many factors should be carefully weighed before any conclusion is reached. If the disease is recognized early in the pregnancy, it is perfectly reasonable to put the patient on treatment and observe her for a period of from four to six weeks before a decision is reached.

A general rule for the management of tuberculosis complicated by pregnancy is that the disease should be treated much more rigidly than the uncomplicated case. For instance, if there is a question of induction of pneumothorax or some other collapse procedure, pregnancy should force the indication, rather than delay it.

In the acute, caseous, pneumonic type of tuberculosis, in which pregnancy is discovered early, I have in the past made a practice of advising interruption of the pregnancy. However, I have frequently seen that, in spite of interruption of the pregnancy and the induction of some form of collapse, the disease has progressed, perhaps more rapidly than it would have otherwise. If patients are past the third month in their pregnancy when tuberculosis is discovered, interruption is rarely, if ever, justified. The disease should be treated rigidly and some form of collapse therapy instituted if it is possible or feasible and the patient allowed to go to term. It is amazing how well patients with far advanced pulmonary tuberculosis tolerate pregnancy. Their condition will frequently improve, or, at least, remain stationary, during the latter months and the patients will go through labor normally. A percentage of them will take a downhill course several months later, but it should be emphasized that this is the natural course of the disease and not necessarily a result of the pregnancy.

Bed rest with adequate nutrition, supplemented by the various collapse procedures, such as pneumothorax, phrenic nerve interruption and thoracoplasty when indicated, forms the basis for the present management of tuberculosis. It has been adequately demonstrated that

tuberculosis when complicated by pregnancy, if properly treated, behaves about as well as though pregnancy had not occurred

At the present writing, there is no chemotherapeutic substance that has been accepted as being of value in the treatment of tuberculosis, whether it is complicated by pregnancy or not. The drugs of the sulfone group are, at the present time, too toxic for clinical use. In the field of antibiotics the future is pregnant with possibilities, but there is as yet no substance of proved, clinical value

In dealing with pregnancy that is complicated by tuberculosis, the question usually arises as to whether or not early induction of labor or cesarean section is advisable. From the standpoint of the physiologist, labor and delivery should be made as easy and short as possible by whichever method, in the opinion of the obstetrician, is the least shocking and in which there is the least amount of trauma to the patient. In our experience patients generally have been allowed to go to term and deliver normally, with the exception of the use of mid or outlet forceps. A general anesthetic, particularly in open cases of tuberculosis, is inadvisable. Caudal anesthesia fulfills the indications and has been quite satisfactory when employed

### CONCLUSIONS

1 Statistical evidence indicates that more than an accidental relationship exists between childbearing and the high tuberculosis incidence and mortality rate during the childbearing period of women.

2 A high percentage of tuberculous women associate the onset of their tuberculosis with a pregnancy. The prenatal clinic is a better than average agent for tuberculosis case finding.

3 Two groups of factors associated with childbearing may influence the course of tuberculosis: (a) Specific. Estrogen has a favorable influence and progesterone an unfavorable influence on resistance to tuberculosis in experimental animals. (b) Nonspecific. Lack of rest, food and sleep may result from pregnancy and its complications and exert an unfavorable influence on tuberculosis.

4 The prognosis of tuberculosis complicated by pregnancy is more dependent on the control of the tuberculosis than on the associated pregnancy.

5 Even though the consensus is that pregnancy is an added hazard to the tuberculous woman, the indiscriminate interruption of pregnancy, because of tuberculosis, does not seem to be justified.

6 With adequate treatment most patients with tuberculosis tolerate pregnancy well.

### BIBLIOGRAPHY

- 1 Krause, A. K.: *Am. Rev. Tuberc.*, 51:254, 1935
- 2 DeLee J. B.: *Yearbook of Obstetrics and Gynecology* 1936, p. 76
- 3 Maternal Mortality. Philadelphia County Medical Society, 1931-1934

- 4 Nichol森, E. E National Tuberculosis Assn Social Res Ser No 4, New York, 1933
- 5 Jamison, E M Am J Obst & Gynec., 36 1, 59-66 (July) 1938
- 6 Eisele and Mason Am J Obst & Gynec, 36 389-392 (Sept) 1938
- 7 Maeder and Myers Am J Obst & Gynec, 40 218-225 (Aug) 1940
- 8 Norris, C C Am J Obst., 73 997, 1916
- 9 Smith, T J.A.M.A., 68 669, 1917
- 10 Mueller, V Casopis Lekaruv Ceskych, 62 34, Prague, 1923
- 11 Burke, H E Surg, Gynec & Obst, 71 615, 1940
- 12 Wade, L J Am Rev Tuber, 46 93-100 (July) 1942
- 13 Steinbach and Klein J Exper Med, 38 656, 1937
- 14 Brack, C B and Gray, L A Endocrinol., 27 322, 1940
- 15 Long, E R and Vogt, A B Am Rev Tuberc, 44 196, 1940
- 16 Carnes, W H and Biskind, G R Bull Johns Hopkins Hosp., 66 297, 1940
- 17 Green, M R and Morgan, R. H Proc Soc. Exper Biol & Med, 38 656, 1938
- 18 Lurie, Max B Personal communication
- 19 Jamison, E. M Gynec and Obst. Tuberculosis Philadelphia, Lea & Febiger, 1935.
- 20 Ornstein and Covnat Am Rev Tuberc, 31 224-232, 1935
- 21 Ornstein and Epstein Quart. Bull Seaview Hosp., 4 420, 1939
- 22 Mariette, Lawson and Litzenberg Am J M Sc, 203 866-874 (June) 1942

# RECENT ADVANCES IN THE MANAGEMENT OF THE SYPHILITIC PREGNANT WOMAN

HERMAN BEERMAN, M.D., Sc.D (MED)\*

AND

NORMAN R. INGRAHAM JR., M.D.†

PREVENTION and treatment of syphilis in the pregnant woman, one of the most efficient approaches of the public health movement to control this disease, has made many advances in the past decade. Within a relatively short time case finding has been stimulated by the enactment in various states of premarital and prenatal examination laws, a better understanding of the fundamental principles of treatment of the syphilitic pregnant woman have been attained, new drugs and methods of treatment have been introduced, and the diagnosis of syphilis in the infant has been placed on a more or less sound foundation. As a result of these advances, practitioners now have at their command practical means for elimination of congenital syphilis.

## PATHOGENESIS OF SYPHILIS IN THE PREGNANT WOMAN

In order to properly treat syphilis in pregnancy it is necessary to know the pathogenesis of the disease in the pregnant woman. There is now general agreement that syphilis is practically exclusively transmitted to the fetus by the mother. This view is based on the following advances in our knowledge of this subject:

1 The mother, if not infected at the time of conception, may readily be inoculated via the uterine cavity. She is invariably infected, therefore, when her child is diseased.

2 The mother has positive blood serologic reactions for syphilis or some other evidence of the disease in *almost* every case in which the child is infected.<sup>1</sup>

3 Most evidence seems to show that the fetus is infected in the later months of pregnancy and not close to the time of conception.

---

From the Department of Dermatology and Syphilology, School of Medicine and the Institute for the Control of Syphilis, University of Pennsylvania (John H. Stokes, M.D., Director).

Assistant Professor of Dermatology and Syphilology, School of Medicine and Graduate School of Medicine, and Assistant Director Institute for the Control of Syphilis, University of Pennsylvania. Assistant Chief of Clinic of Cutaneous Medicine and Syphilology, University of Pennsylvania Hospital.

† Assistant Professor of Dermatology and Syphilology, School of Medicine and Associate Director Institute for the Control of Syphilis, University of Pennsylvania. Chief of Syphilis Clinic, Philadelphia General Hospital. Chief Division of Venereal Disease Control, Department of Public Health, Philadelphia.

These facts may be summarized as follows (a) Spontaneous abortion (prior to the fourth month of gestation) occurs with about the same frequency among syphilitic and nonsyphilitic mothers. Similarly, late miscarriage has a noticeably greater incidence among known syphilitic parents. (b) Antepartum therapy for syphilis can assure the birth of a healthy infant in almost 100 per cent of cases, if it is continued throughout the later half of pregnancy only. (c) No embryo which contained spirochetes has been shown prior to the sixteenth week of fetal life (cf Hoffmann, Dippel<sup>2</sup>). Histologic changes in the embryo suggestive of syphilis have been described prior to the fourth month but *Spirochaeta pallida* has not been found, which must cast some doubt on the syphilitic nature of these lesions. (d) Syphilitic skeletal changes have not been shown to occur prior to the sixth lunar month, which would indicate that infection of the fetus had occurred not earlier than the fourth lunar month<sup>3</sup>.

The maternal portion of the placenta may be infected as a result of the occasional showers of *Spirochaeta pallida* which gains access to the blood stream of the mother, as in any active syphilitic infection. In general, the more recent the mother's infection with syphilis, the longer, more intense the bouts of spirochetemia and therefore, the greater the chance of infection of the fetus<sup>4</sup>.

#### DIAGNOSIS OF SYPHILIS IN THE PREGNANT WOMAN

The pregnant woman with syphilis is usually unaware of her infection. If history alone is depended on, about 90 per cent of the cases would be lost. It is not only because of poor observation on the part of the mother that she may not know she is diseased, but because the early manifestations themselves may be rather insignificant. The initial lesion may be on the cervix, labial lesions may be small and painless, or no lesions may appear at any time, and pregnancy may have a definitely modifying effect on the development of the florid lesions. Accordingly, routine blood testing of all pregnant women, as recognized in the prenatal blood test laws, becomes a matter of great moment. Various authors have found signs, symptoms or history of syphilis in 25 to 64 per cent of mothers. The points in the history which Ingraham (1935) found to be of greatest value were (1) treatment prior to pregnancy (46 per cent), (2) occurrence of late miscarriage or neonatal death in earlier pregnancies (35 per cent), (3) story of symptoms suggestive of syphilis (25 per cent), and (4) syphilis in other members of the family (21 per cent). Diagnostic physical signs of syphilis were present in the mother in only 10 per cent, but there was suggestive evidence in an additional 13 per cent.

The serologic tests on syphilitic pregnant women will give results depending on the age of the syphilis in the patient. The earlier the infection, the higher the proportion of positive results. Young women are more likely to have an untreated recently acquired infection in

which positive laboratory findings are readily obtained. The serologic tests in syphilis are generally reliable. The strongly positive serologic reaction in the pregnant woman, verified on repetition, is diagnostic of the disease. Women with doubtful or weakly positive serologic reactions during pregnancy with no other evidence of the disease and negative history will in the majority of cases show no evidence of syphilis, even on prolonged study. This is not different from the same situation when doubtful reactions are encountered in nonpregnant healthy individuals in whom the disease is never proven. Stokes and Ingraham<sup>6</sup> found, from the Philadelphia General Hospital material, that the diagnostic error in terms of positive reactions from causes other than active syphilis based on follow-up of the infants of these untreated mothers was less than one per cent.

The question of biologic false positive reactions in syphilis has had some recent discussion in the literature (Beerman<sup>6</sup>). Spiegler found only 0.45 per cent positive reactions among 6580 patients. In the 1934 serology conference, the standard tests with the exception of the Hinton, gave no such reactions in fifty-four patients. The Hinton test yielded a very small number of such reactions. Kandler in 1940 concluded from an experience of 10,354 pregnant women, that there is no evidence that pregnancy impairs the sensitivity or specificity of the tests. Our experience concurs with this conclusion.

In view of the relative reliability of the serologic tests for syphilis in pregnancy, the practice of performing routine blood serologic tests for syphilis on every pregnant woman at the time of her first prenatal visit, as is required by many states, has uncovered a number of patients with latent syphilis and has given us the first reliable data on the incidence of syphilis in the pregnant woman. One such survey, based on 48,800 routine antepartum blood tests on the general population in New Jersey, showed 1.19 positive results. The taking of a single blood test at the time of the first prenatal visit, as desirable and valuable as it is, will not uncover all syphilis in pregnancy. Syphilis may be acquired at the time of conception, or even in the later months of pregnancy. Such women may or may not present symptoms, depending upon the duration of their infections and the development of the normal clinical course of their disease, prior to delivery. Therefore, a negative serologic reaction early in pregnancy should not exclude syphilis, especially if suspicious signs develop at a later date. To uncover all these cases, it is recommended that every pregnant woman have, in addition to the blood test at the time of the first prenatal visit, a repetition of this test at or near term.

#### TREATMENT OF SYPHILIS IN PREGNANCY

For the past two decades, numerous authorities (Williams 1920, McCord 1930, 1935, Jeans and Cooke 1930, McKelvey and Turner 1934, Cole, et al 1934, 1936, Ingraham 1938, Halloran 1939, Dill, Stander

and Isenhour 1940, Benensohn 1942, Boas and Gammeltoft in Denmark, Nabarro and Findlay in England, Hoffman in Germany) have shown that syphilis transmitted from parent to offspring is practically a preventable disease and that its prevention depends upon diagnosis and treatment of syphilis in the pregnant woman. In order to have effective treatment, a drug which has strong spirillicidal action must be used. Such preparations are neoarsphenamine, arsenoxide (mapharsen, dichlorophenarsine hydrochloride) or the newly introduced penicillin. Heavy metals alone, bismuth or mercury, are ineffectual. Recent observations have indicated that certain principles must be followed in the treatment of the syphilitic pregnant woman if the greatest advantage is to be obtained from the antisyphilis remedies. These principles are given as follows:

#### PRINCIPLES OF TREATMENT OF THE SYPHILITIC PREGNANT WOMAN\*

- 1 Begin treatment of the syphilitic pregnant woman as soon as the diagnosis is established. A delay of even a few days may mean a syphilitic child.
- 2 To be effective the drug must be spirillicidal. Intravenous neoarsphenamine and mapharsen have been most thoroughly tried. Penicillin alone or in combination with these may rapidly supplant the older types of therapy.
- 3 Protection of the child is the primary aim of treatment during pregnancy. No treatment should be used which is likely to be injurious to either mother or fetus. If necessary the syphilis may be cured in the mother after delivery.
- 4 Treat largely with spirillicidal drugs during the late months. The fetus is seldom infected prior to the twentieth week. Treatment may be largely with heavy metal in the arsenic bismuth regimen in the early months.
- 5 Reduce the initial dose of spirillicidal drug if treatment is begun after the fifth month. The first injection may be 0.2 gm of neoarsphenamine (or its equivalent), the average dosage for the first three weeks should not exceed 0.3 gm of neoarsphenamine per week. Total weekly dosage need never exceed 0.45 gm for the 150-pound adult. (For penicillin regimen see text.)
- 6 Continuous alternating is preferred to concurrent treatment if arsenic-bismuth regimens are used.
- 7 After the fifth lunar month the length of the bismuth course should not exceed four to six weeks, lest infection of the fetus result from lack of spirillicide.
- 8 Treatment should be continuous. No rest interval.
- 9 Arsenal should be given for four to six weeks immediately before delivery.
- 10 If reactions occur, stop treatment and reevaluate. Do not injure the mother with overzealous applications of treatment for the unborn child. The average pregnant woman tolerates normal antisyphilitic therapy well but, should reactions occur, they may be serious and should not be considered lightly.

\* Modified from Stokes, Beerman and Ingraham, "Modern Clinical Syphilology," W B Saunders Company, 1944, p 1150, Fig 847

In the treatment of the syphilitic pregnant woman, the dosage of the arsenical need not exceed 0.45 gm of neoarsphenamine, or an equivalent amount of arsenoxide. Because of the conflicting results obtained by different observers with mapharsen, it is best to use it in dosage up to 0.05 gm every five days (Astrachan 1940,<sup>7</sup> Minnich 1941,<sup>8</sup> Castallo et al 1939,<sup>9</sup> Soule and Bortnick 1943<sup>10</sup>). It is never too late to begin treatment for syphilis in pregnancy. A few treatments in the latter months of pregnancy may mean the difference between a syphilitic and nonsyphilitic baby. If there is any reasonable doubt that the mother is cured of her disease a syphilitic woman should be treated during every pregnancy, irrespective of the amount of treatment received previously and irrespective of the apparent clinic status. For many years the effective treatment of syphilis and the test of clinical cure has been such that this dictum has been essential and almost uniformly taught and followed. The apparent success of some of the more intensive methods of therapy in completely eradicating the syphilis from the patient leave serious doubt as to whether treatment is always necessary. It is still good practice, however to treat in each subsequent pregnancy if in doubt.

One of the more recent advances in the treatment of early acquired syphilis is *massive dose* chemotherapy with the arsenoxides (mapharsen, dichlorophenarsine hydrochloride) by the five day drip method or by a syringe technic and fever induced by typhoid vaccine. This has been tried in the pregnant woman and favorable reports, based on small numbers of cases of the efficacy of both methods have appeared (Sadusk and Shaffer 1942,<sup>11</sup> Benenson 1942,<sup>12</sup> Rattner 1943,<sup>13</sup> Speiser, Wexler, Thomas and Asher 1945<sup>14</sup>). Speiser and his co-workers found that massive mapharsen therapy in the treatment of early infectious syphilis prior to the onset of pregnancy gave excellent results since there was only one failure among thirty-two patients so treated. We feel that these methods are not indicated because of the excellent results normally obtained with more conservative treatment and especially penicillin, as well as the increased risk to the mother (fatal encephalopathy, one case in forty-three patients treated, Speiser et al., 1945) when the more intensive methods are used.

#### CONTROL OF TREATMENT REACTIONS TO ARSENOTHERAPY

During pregnancy treatment for syphilis should be accompanied by exceedingly careful obstetrical prenatal care. Ingraham, Ingraham, Beerman, Spence, Arnold and Hassler<sup>15</sup> have pointed out the value of having separate clinics for the pregnant syphilitic woman where these are practical. Pregnant women under treatment for syphilis should have weekly urinalyses and blood pressure determinations. Careful inquiry and inspection by a physician should be made to elicit any complaints from the patient which indicate circulatory embarrassment or kidney insufficiency. With careful attention to detail reactions to treatment



have been found to be infrequent and for the most part inconsequential. An extensive literature has accumulated on the subject of treatment reactions in syphilitic pregnant women, and a small number of deaths usually from acute hemorrhagic encephalopathy associated with arsenotherapy have been reported (Ingraham 1939,<sup>16</sup> cf Moore 1939,<sup>17</sup> Plass and Sacks, 1942,<sup>18</sup> Kennedy and Hennington, 1943<sup>19</sup>)

It is difficult to set arbitrary rules to cover all complications of syphilotherapy when they arise. Individual case problems should be decided upon only after competent obstetrical and syphilologic consultation. One of the problems with acute hemorrhagic encephalopathy has been its simulation of the comas and convulsive states of the toxemias of pregnancy, and failure of recognition of the true situation until it was too late or until death had actually occurred. A constant awareness of this possibility is essential. We believe that, in general, treatment should be withheld until competent appraisal of the situation is possible under the following circumstances: (1) if the woman's blood pressure, which has been normal, increases to exceed 150/100, (2) if vaginal bleeding, hematuria, purpura or other hemorrhagic phenomena (hematopoietic injury) occur, (3) if there is jaundice or other evidence of liver damage, (4) if severe headache, visual disturbances or other evidence of central nervous system involvement become manifest (hemorrhagic encephalopathy), or (5) if the woman reports with a temperature of more than 100° F.

#### TREATMENT OF THE PREGNANT SYPHILITIC WOMAN WITH PENICILLIN\*

If the preliminary results with penicillin in the prevention of congenital syphilis are borne out by our rapidly accumulating knowledge, this drug may supplant all others in the treatment of the syphilitic pregnant woman. Thus far, our information is limited to data collected from relatively small numbers of women, largely with symptomatic early syphilis whose infant offsprings have been followed for periods of a year or less postnatally. The bulk of the problem, namely the effect of penicillin on the pregnant woman with latent syphilis of unknown duration, remains largely an untouched field. On the other hand, the highest percentage of syphilitic babies come from women whose disease is of recent origin and it is a reasonable assumption that treatment which is effective in preventing the transmission of the infection in its severest form from mother to fetus will be equally effective in preventing the passage during the latent and late stages of the disease.

We would like first to present a case report, illustrating in detail the actual response of early syphilis in pregnancy to penicillin and then to discuss the present status of our knowledge of the use of this

\* The work described in this section was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Pennsylvania.

drug to prevent congenital syphilis. This case was presented in part (Case No 13) in our original article on 'Penicillin in the Prevention and Treatment of Congenital Syphilis,'<sup>20</sup> but considerably more data have been collected since this publication and the woman has gone through another pregnancy.

Secondary Syphilis with Pregnancy Treated with Penicillin Second Pregnancy One Year Later without Treatment Both Children Normal—M. S., a Negress, 29 years of age, was in the sixth lunar month of her fourth pregnancy when she reported to the prenatal clinic of the Philadelphia General Hospital December 15, 1943 with secondary syphilis. Two previous pregnancies in 1940 and 1942 re-

# RESULTS FOLLOWING PENICILLIN THERAPY IN SECONDARY SYPHILIS WITH PREGNANCY

Days Post Penicillin	Mother's Serologic Test in Kline Units	Days after Delivery	Serologic Test, Kline Units	Clinical Notes
0	128			Darkfield positive for <i>Spirochaeta pallida</i> from vulvar lesions at the commencement of therapy (8.30 A.M.) at 12.30 P.M. and at 4.30 P.M. Darkfield negative for <i>Spirochaeta pallida</i> at 8.30 P.M., 12.30 A.M. (Dec. 17) and 4.30 A.M. Lesions completely healed except for pigmentary remains in 72 hours.
9	128			
12	64			
26	32			
68	16			
89	2			
96	4			

## First Infant

104	4	0 (Delivered 3/29/44)	0.5	Weight 6 lb. 2 1/4 oz. Darkfield of umbilical vein negative. Physical examination of infant normal. Roentgenogram of long bones negative.
124	16	20	Neg.	
141	Neg.	37	Neg.	Physical examination of infant normal.
139	Neg.	35	Neg.	
173	0.5	69	Neg.	Roentgenogram of long bones negative.
224	Neg.	83	Neg.	
237	Neg.	183	Neg.	Roentgenogram of long bones negative.
245	Neg.	234	Neg.	
393	Neg.	299	Neg.	Normal physical examination.
416	Neg.			
470	Neg.			

## Second Infant

		0 (Delivered 3/29/43)		Normal physical examination. Roentgenogram of long bones normal. Negative physical examination and roentgenogram of long bones normal.
311	Neg.	4	Neg.	
344	Neg.	85	Neg.	

spectively had been delivered by cesarean section because of cephalopelvic disproportion. A third pregnancy resulted in an abortion in February 1943. The exact duration of her syphilis was unknown, but her presenting symptoms consisted of a maculo-papular eruption scattered over the thorax and extremities, split papules at the angles of her mouth and numerous small condylomata lata.

on the vulva which revealed numerous *Spirochaeta pallida* to darkfield examination. It was assumed that her infection was acquired in the early months of the pregnancy and was not more than of two or three months' duration. She was admitted to the Hospital of the University of Pennsylvania on December 15, and started on treatment with sodium penicillin 25,000 Oxford units every four hours intramuscularly at 8:30 A.M. on December 16. The drug was dissolved in 2 cc. of distilled water for administration. The course from then on is shown in the accompanying outline.

The method of treating the syphilitic pregnant woman with penicillin has been borrowed largely from published experience with the treatment of early syphilis in the adult.<sup>1</sup> The material about to be presented in the discussion represents the studies of the Syphilis Penicillin Panel of the Hospital of the University of Pennsylvania with forty-nine syphilitic pregnancies treated with penicillin between November 19, 1943 and May 26, 1945.

The initial clinical response seen in the case presented is similar to that found in the treatment of all patients with early syphilis with penicillin. *Spirochaeta pallida* is seldom demonstrable in the open lesion for longer than twelve hours after the institution of treatment and the lesions themselves are ordinarily completely healed before treatment is completed (i.e., within a one week period). This patient exhibited a moderate febrile Herxheimer reaction, her temperature fluctuating between 99° F. and 101° F. for the second and third day of treatment. This is likewise an almost uniform occurrence in pregnant women with early syphilis as with all cases of freshly acquired syphilis treated with penicillin.

The therapeutic shock at the commencement of treatment in the pregnant woman with early syphilis may occasionally, in our experience, be harmful to the fetus. Accompanying the febrile reaction a large percentage of our cases have had abdominal pain, gastrointestinal disturbances and in an occasional instance, symptoms of threatened abortion, with lower abdominal cramps and vaginal bleeding. One of the women in this series miscarried during the course of treatment and in another instance it was necessary to stop the treatment entirely and to continue therapy some weeks later after symptoms of threatened miscarriage had subsided. These various occurrences, though certainly not a contraindication to the treatment of the syphilitic pregnant woman with penicillin, have made us feel that reduction of the initial dosage is desirable for at least the first forty-eight hours. The dosage should be reduced by approximately three-fourths for the first day of treatment and by one-half for the next day, to be continued in full dosage on the third or fourth days and for the remainder of the course. We have not seen any complications from penicillin occurring in the latter half of the penicillin course.

Our experience would indicate that a total dosage of either 12 million or of 24 million Oxford units of sodium penicillin is satis-

factory both to prevent infection of the fetus and to cure the disease in the mother. This total dosage is preferably given in individual injections intramuscularly of 20 000 units (for 12 million unit courses) or of 40,000 units (for 24 million unit courses), every three hours. Specifically, if a 24 million unit total dosage were decided upon and the individual doses were reduced during the first forty-eight hours, the woman would then receive

- 10,000 Oxford units sodium penicillin intramuscularly every three hours for 8 doses, followed by
- 20 000 Oxford units sodium penicillin intramuscularly every three hours for 8 doses, followed by
- 40,000 Oxford units sodium penicillin intramuscularly every three hours for 54 doses.

The total treatment course would occupy from eight to nine days. If it were desired to shorten the course then dosage per injection on the last day or two could be increased. We, however, prefer the longer course and the higher dosage (i.e., 24 million Oxford units) since we believe that the pregnant syphilitic woman should be given every possible chance to give birth to a healthy child and that there should not be unnecessary risks resulting from reduced dosage or foreshortened courses. The only penicillin failure we have experienced thus far in the sense that the infant was infected in treating a woman with early syphilis, has been in a patient who received 1.2 million Oxford units of sodium penicillin in a period of four days. This mother had the combined disadvantage of the lower dosage and the shorter interval of treatment. She was not cured of her syphilis, relapsed infectiously, and transmitted the disease to her infant at about the time of delivery.

The above data indicate the degree of success we have had thus far with the treatment of the pregnant syphilitic woman to prevent congenital syphilis. Twenty-seven of the women treated have thus far been delivered and their babies have been followed for periods of two months to more than a year postnatally. Repeated physical examinations, blood serologic tests and roentgenograms of the long bones have failed to reveal evidence of syphilis in any except the one case above mentioned. These results, in the neighborhood of 95 per cent satisfactory, are at least as good, in fact, better than the average obtained with other modes of treatment.

It will be noted in the case report that the patient was still sero-positive at term. A negative blood serologic reaction for syphilis by the time of delivery is not essential to the birth of a healthy infant. In fact, in only seven instances, among the forty pregnant women in our series who have thus far been carried through to term, was the mother's blood negative at the time of birth of her child. Thirty-eight per cent of our apparently healthy infants also had positive cord and neonatal Wassermanns. These uniformly reverted to negative in most instances by the age of three or four weeks so that they apparently

represented a transfer of syphilis reagin from mother to child rather than infection of the fetus

Whether penicillin will traverse the placental barrier and cure an already infected fetus is still a matter for speculation. Penicillin has been shown to permeate the placenta at term and has been recovered from the newborn infant when the mother has been treated during labor.<sup>22</sup>

Of more interest from our standpoint, however, is the question of permeation of the placenta from the fourth to the ninth lunar months, since the fetus may be infected at any time during this period and since previous studies have shown that the permeability of the placenta is not uniform throughout the pregnancy. Some of our women have been treated prior to the sixteenth week, the majority between the sixteenth and thirty-second week, but a few later than the thirty-second week, all with uniformly good results. This suggests clinically that penicillin may readily permeate the placenta during all the latter months of the pregnancy though we cannot be certain of this point without a considerably longer period of study.

The fact of greatest interest, perhaps, in the case reported is that the patient has completed a second pregnancy, approximately sixteen months after receiving her course of penicillin for early syphilis and that preliminary investigation of the infant at least, covering a period of twelve weeks postnatally, indicates that he is normal. If a single course of penicillin will cure syphilis to the extent that we may disregard the long-established and much reiterated dictum of re-treatment in every pregnancy once syphilis is established, we will have made a great step forward in the management of the syphilitic mother. It will take many more cases to establish this fact, but the present instance is at least very encouraging.

#### EVALUATION OF THE EFFECTIVENESS OF TREATMENT IN THE SYPHILITIC PREGNANT WOMAN

In the last analysis, the effectiveness of antisyphilitic treatment of the pregnant woman is indicated by the presence or absence of syphilis in the newborn or the lack of adverse effect of antenatal treatment on fetal mortality. The consensus of recent contributions to this latter problem is that no definite fetal mortality rate could be associated with adequate antenatal therapy for syphilis.<sup>23</sup> With regard to diagnosis of syphilis in the newborn, most recent studies agree that the cord blood has little true diagnostic value, and cannot be depended on to decide whether or not the offspring of the syphilitic mother is infected. It may contain syphilis reagin and give a positive serologic test in the normal infant of a seropositive syphilitic mother, it may be negative even though the infant is diseased. This circumstance is not peculiar to the cord blood, but is equally true of the infant's blood during the

neonatal period. The cord or neonatal blood test result on the newborn is of value largely as a baseline for future determinations. As the result of a survey of the literature and numerous personal observations, we believe the offspring of the syphilitic mother may be considered to be infected when

- 1 *Spirochaeta pallida* is demonstrated in skin or mucous membrane lesions or in scrapings from the umbilical vein (Ingraham <sup>4</sup>)
- 2 The blood serologic reactions of the tests for syphilis are strongly positive on repetition after the third month of life. Prior to the third month, in the absence of clinical symptoms it is difficult to establish a definite diagnosis without a knowledge of the mother's and infant's serologic reactions at birth and without the use of quantitative titrated tests. If such information is available then the following additional criteria for diagnosis are applicable in determining infection of the infant.
  - (a) The titer of the blood serologic reactions of the newborn child is significantly greater than that of the mother (or positive when the mother's reactions are negative)
  - (b) The titer of the infant's blood serologic reactions rapidly increases after birth (or reactions negative at birth subsequently develop a sustained positivity)
- 3 A properly interpreted roentgenogram of the long bones in a sero-positive infant during the first eight weeks of life which shows an unquestionable (preferably advancing) osteochondritis with or without periostitis (Ingraham, Shaffer, Spence and Gordon 1941<sup>23</sup>)

#### SUMMARY

Congenital syphilis can all but completely be prevented by treatment of the syphilitic pregnant woman. The detection of syphilis in the pregnant woman is not always easy because of the meagerness of the symptomatology of the disease during pregnancy and because of the failure, at times, of the physician to use every available resource at his command. Since infection of the fetus may occur prior to the fifth lunar month of pregnancy, the earlier diagnosis of syphilis in the mother is made, the more chance the infant has of escaping infection, provided treatment is instituted as soon as the disease is discovered.

Almost all syphilis in pregnancy is discovered by the routine use of the blood serologic tests. A test early in pregnancy will detect ante-conceptionally acquired syphilis but a repetition of the test made near the time of delivery (seventh to eighth month) will be necessary to detect infections occurring during the early months of pregnancy. While occasionally there may be false positive reactions in the blood in pregnancy there is just as much likelihood of false negative reactions. On the whole, the blood tests are just as reliable in pregnancy as in other phases of syphilis. New methods of blood serologic

(Kahn verification test, etc.) have not eliminated the distrust felt by some in blood tests during pregnancy

Other aids in diagnosis of syphilis in pregnancy are the careful history and physical examination. These procedures are especially necessary in cases of seronegative syphilis in pregnant women. For practical purposes of diagnosis, it is recommended that blood tests be made routinely on every pregnant woman early in the pregnancy and that, if they are negative, they be repeated later (at term, if not in the last months of the pregnancy).

If syphilis is discovered in the pregnant woman, the possibility of the fetus becoming infected depends on several factors. The more recent the infection in the mother, the more liable is the child to be syphilitic. The child born of a syphilitic mother with a negative blood serologic test is less apt to be infected with syphilis than is one born of a seropositive mother. The amount and kind of prenatal therapy and the time at which it is instituted in the pregnant woman are factors of the utmost importance in the question of transmission of syphilis from the mother to her offspring. Treatment begun at or about the fourth month of pregnancy and continuing at weekly intervals to total not less than 4 gm of arsenical (neoarsphenamine) or the equivalent of arsenoxide with or without heavy metal (bismuth subsalicylate) constitutes about optimal conditions for the prevention of prenatal syphilis.

This type of treatment may be supplanted, in early acquired infections at least, by 2.4 million Oxford units of sodium penicillin intramuscularly given in individual dosage of approximately 40,000 units each every three hours over an interval of from eight to nine days. Preliminary results with limited numbers of cases indicate a degree of success with this type of treatment at least equal to that obtained from the arsenical bismuth regimens. The mother is moreover apparently cured of her disease by this single short course of therapy.

Pregnant women tolerate arsenical and heavy metal treatment well. One must not overlook the fact, however, that these individuals do occasionally show serious reactions to the arsenicals, and treatment should be adjusted accordingly. A urine examination and blood pressure determination before each arsenical injection are of the utmost importance. The aim of treatment is not to cure syphilis in the pregnant woman but to prevent syphilis in the offspring. From this point of view, syphilis in pregnancy is early syphilis and the drugs most effective in early syphilis are the strongly spirillicidal drugs. The arsenicals, neoarsphenamine (0.45 to 0.6 gm at weekly intervals), mapharsen (0.04 to 0.06 gm at five day intervals) or penicillin (for exact dosage see body of paper) may be used in accordance with the physician's convenience. Bismuth subsalicylate in dosage of 0.2 gm (about 120 mg of metallic bismuth) is the heavy metal of choice where it is desirable to use this type of drug. In the arsenic-bismuth regimen,

treatment should be alternating and continuous and it should be so arranged that the predelivery therapy be arsenical. If treatment is begun after the fifth month, it should start with an arsenical. In case of reaction, treatment should be individualized.

Examination of the cerebrospinal fluid wherever necessary should be deferred until after delivery. In all of our services the test is made just before discharge from the maternity hospital.

The newer intensive methods of chemotherapy (five day continuous intravenous drip and syringe technic employing multiple injections) have not had adequate trial in the treatment of the pregnant woman and the dangers of toxicity are not fully worked out.

#### BIBLIOGRAPHY

1. Ingraham, N. R., Jr. and Kahler, J. E. The Diagnosis and Treatment of Syphilis Complicating Pregnancy. *Am. J. Obst. & Gynec.*, 27:134, 1934.
- Ingraham, N. R., Jr. The Diagnosis of Infantile Congenital Syphilis During the Period of Doubt. *Am. J. Syph. & Neurol.*, 19:547, 1935.
2. Hoffman, E. Congenital Syphilis. *Am. J. Syph., Gonorr. & Ven. Dis.*, 22:198, 1938.
- Dippel, A. L. The Relationship of Congenital Syphilis to Abortion and Miscarriage and the Mechanism of Intrauterine Protection. *Am. J. Obstet. & Gynec.*, 47:369, 1944.
3. Ingraham, N. R., Jr. The Lag Phase in Early Coongenital Osseous Syphilis. *Am. J. M. Sc.*, 121:819, 1936.
4. Cole, H. N. and Jeans, P. C. et al. Syphilis in Mother and Child. Supplement No. 7 to *Ven. Dis. Inform.*, 1940.
5. Stokes, J. H. and Ingraham, N. R., Jr. Diagnosis and Treatment of Congenital or Prenatal Syphilis. *M. CLIN. NORTH AMERICA*, 23:1575 (Nov.) 1939.
6. Beerman, H. Biologic False Positive Reactions to the Tests for Syphilis, Pt. II. *Am. J. M. Sc.*, Oct., 1945.
7. Astrachan, G. D. Syphilis in Pregnancy. *New York State J. Med.*, 40:43-50, 1940.
8. Minnich F. R. Treatment of Syphilis in Pregnancy. *Am. J. Obst. & Gynec.*, 42:159, 1941.
9. Castallo M., Coppolino, J., Rakoff A., Roeder, P. and Dickson G. Mapharsen in Treatment of Syphilis Complicating Pregnancy. *Am. J. Syph., Gonorr. & Ven. Dis.*, 23:332, 1939.
10. Soule, S. D. and Bortnick, A. R. Mapharsen in Syphilis Complicated by Pregnancy. *Missouri State M. A.*, 40:97-99, 1943.
11. Sadock, J. F., Jr. and Shaffer T. E. Observation on the Massive Dose Arsenotherapy of Early Syphilis by the Intravenous Drip Method. III. Pregnancy and Its Outcome, Associated With or Following the Treatment of Early Syphilis by Massive Arsenotherapy. *Yale J. Biol. & Med.*, 14:365-371, 1942.
12. Benenson, S. J. Pregnancy in the Syphilitic Mother—935 Pregnancies. *Am. J. Obst. & Gynec.*, 43:508, 1942.
13. Rattner H. The Treatment of Syphilis in Pregnancy by the Five Day Massive Dose Method. *Am. J. Obst. & Gynec.*, 46:255-259, 1943.
14. Speiser M. D., Weder G., Thomas, E. W. and Asher H. A. The Rapid Treatment of Early Syphilis During Pregnancy. *Am. J. Obst. & Gynec.*, 49:214-225, 1945.
15. Ingraham, L. B., Ingraham, N. R. Jr., et al. The Prevention of Coongenital



(Kahn verification test, etc.) have not eliminated the distrust felt by some in blood tests during pregnancy

Other aids in diagnosis of syphilis in pregnancy are the careful history and physical examination. These procedures are especially necessary in cases of seronegative syphilis in pregnant women. For practical purposes of diagnosis, it is recommended that blood tests be made routinely on every pregnant woman early in the pregnancy and that, if they are negative, they be repeated later (at term, if not in the last months of the pregnancy).

If syphilis is discovered in the pregnant woman, the possibility of the fetus becoming infected depends on several factors. The more recent the infection in the mother, the more liable is the child to be syphilitic. The child born of a syphilitic mother with a negative blood serologic test is less apt to be infected with syphilis than is one born of a seropositive mother. The amount and kind of prenatal therapy and the time at which it is instituted in the pregnant woman are factors of the utmost importance in the question of transmission of syphilis from the mother to her offspring. Treatment begun at or about the fourth month of pregnancy and continuing at weekly intervals to total not less than 4 gm of arsenical (neoarsphenamine) or the equivalent of arsenoxide with or without heavy metal (bismuth subsalicylate) constitutes about optimal conditions for the prevention of prenatal syphilis.

This type of treatment may be supplanted, in early acquired infections at least, by 2.4 million Oxford units of sodium penicillin intramuscularly given in individual dosage of approximately 40,000 units each every three hours over an interval of from eight to nine days. Preliminary results with limited numbers of cases indicate a degree of success with this type of treatment at least equal to that obtained from the arsenical bismuth regimens. The mother is moreover apparently cured of her disease by this single short course of therapy.

Pregnant women tolerate arsenical and heavy metal treatment well. One must not overlook the fact, however, that these individuals do occasionally show serious reactions to the arsenicals, and treatment should be adjusted accordingly. A urine examination and blood pressure determination before each arsenical injection are of the utmost importance. The aim of treatment is not to cure syphilis in the pregnant woman but to prevent syphilis in the offspring. From this point of view, syphilis in pregnancy is early syphilis and the drugs most effective in early syphilis are the strongly spirillicidal drugs. The arsenicals, neoarsphenamine (0.45 to 0.6 gm at weekly intervals), mapharsen (0.04 to 0.06 gm at five day intervals) or penicillin (for exact dosage see body of paper) may be used in accordance with the physician's convenience. Bismuth subsalicylate in dosage of 0.2 gm (about 120 mg of metallic bismuth) is the heavy metal of choice where it is desirable to use this type of drug. In the arsenic-bismuth regimen,

treatment should be alternating and continuous and it should be so arranged that the predelivery therapy be arsenical. If treatment is begun after the fifth month, it should start with an arsenical. In case of reaction, treatment should be individualized.

Examination of the cerebrospinal fluid wherever necessary should be deferred until after delivery. In all of our services the test is made just before discharge from the maternity hospital.

The newer intensive methods of chemotherapy (five day continuous intravenous drip and syringe technic employing multiple injections) have not had adequate trial in the treatment of the pregnant woman and the dangers of toxicity are not fully worked out.

#### BIBLIOGRAPHY

1. Ingraham, N. R., Jr and Kahler J. E. The Diagnosis and Treatment of Syphilis Complicating Pregnancy. *Am. J. Obst. & Gynec.*, 27 134 1934
- Ingraham, N. R. Jr., The Diagnosis of Infantile Congenital Syphilis During the Period of Doubt. *Am. J. Syph. & Neurol.*, 19 547 1935
2. Hoffman, E. Congenital Syphilis. *Am. J. Syph., Gonorr. & Ven. Dis.*, 22 198 1938
- Dippel, A. L., The Relationship of Congenital Syphilis to Abortion and Miscarriage and the Mechanism of Intrauterine Protection. *Am. J. Obstet. & Gynec.*, 47 369, 1944
3. Ingraham, N. R., Jr. The Lag Phase in Early Congenital Osseous Syphilis. *Am. J. M. Sc.*, 191-819 1936
4. Cole, H. N. and Jeans P. C. et al. Syphilis in Mother and Child. Supplement No 7 to *Ven. Dis. Inform.*, 1940
5. Stokes, J. H. and Ingraham, N. R., Jr. Diagnosis and Treatment of Congenital or Prenatal Syphilis. *M. CLIN. NORTH AMERICA*, 23 1575 (Nov) 1939
6. Beerman, H. Biologic False Positive Reactions to the Tests for Syphilis, Pt. II. *Am. J. M. Sc.*, Oct., 1945
7. Astrachan, G. D. Syphilis in Pregnancy. *New York State J. Med.*, 40 43-50 1940
8. Minnich, F. R. Treatment of Syphilis in Pregnancy. *Am. J. Obst. & Gynec.*, 47 159 1941
9. Castillo M., Coppolino J., Rakoff A., Roeder P. and Dickson, G. Mapharsen in Treatment of Syphilis Complicating Pregnancy. *Am. J. Syph., Gonorr. & Ven. Dis.*, 23 332 1939
10. Soole, S. D. and Bortnick, A. R. Mapharsen in Syphilis Complicated by Pregnancy. *Missouri State M. A.*, 40 97-99 1943
11. Sadock, J. F., Jr and Shaffer T. E. Observation on the Massive Dose Arsenotherapy of Early Syphilis by the Intravenous Drip Method III Pregnancy and Its Outcome, Associated With or Following the Treatment of Early Syphilis by Massive Arsenotherapy. *Yale J. Biol. & Med.*, 14 365-371 1942.
12. Benzelsohn, S. J.: Pregnancy in the Syphilitic Mother—935 Pregnancies. *Am. J. Obst. & Gynec.*, 43 508 1942
13. Ratner H. The Treatment of Syphilis in Pregnancy by the Five Day Massive Dose Method. *Am. J. Obst. & Gynec.*, 46 235-259 1943
14. Spenser M. D., Wexler G., Thomas, E. W. and Asher H. A. The Rapid Treatment of Early Syphilis During Pregnancy. *Am. J. Obst. & Gynec.*, 49 214-225 1945
15. Ingraham, L. B., Ingraham, N. R. Jr., et al. The Prevention of Congenital

- Syphilis in the Large Urban Hospital Am J Syph., Gonorr & Ven Dis., 25 731, 1941
- 16 Ingraham, N R., Jr Complications Due to Arsenical Therapy in Syphilitic Pregnant Women, Report of Seven Maternal Deaths J.A.M.A., 112 1537-1543, 1939
  - 17 Moore, J E. Editorial Arsenical Reactions in Pregnant Women Am J Syph., Gonorr & Ven Dis., 23 518-522, 1939
  - 18 Plass, E. D and Sacks, N Syphilis in Obstetrics Am J Obst. & Gynec., 43 484-492, 1942
  - 19 Kennedy, C. B and Hennington, V M Complications of Antisyphilitic Therapy in Pregnancy Arch Dermat. & Syph., 48 83-87, 1943
  - 20 Lentz, J W., Ingraham, N R., Jr., Beerman H and Stokes, J H Penicillin in the Prevention and Treatment of Congenital Syphilis J.A.M.A., 126 408 (Oct 14) 1944
  - 21 Mahoney, J F, Arnold, R. C and Harris, A. Penicillin Treatment of Early Syphilis A Preliminary Report Ven Dis Inform., 24 355 (Dec) 1943  
Moore, J E., Mahoney, J F., Schwartz, W., Sternberg, T and Wood, W B The Treatment of Early Syphilis with Penicillin J.A.M.A., 126 67 (Sept 9) 1944
  - 22 Herrell, W E., Nichols, D R and Heilman, Dorothy H Penicillin, Its Usefulness, Limitations, Diffusion and Detection with an Analysis of 150 Cases in Which It was Employed J.A.M.A., 125 103 (Aug 12) 1944  
Greene, H J and Hobby, G L Transmission of Penicillin Through Human Placenta. Proc Soc Exper Biol & Med, 57 282 (Nov) 1944
  - 23 Dill, L V, Stander, H J and Isenhour, C. E An Evaluation of the Effect of Antenatal Antisyphilitic Therapy on Mortality and on Congenital Syphilis Am J Obst. & Gynec., 40 965-979, 1940
  - 24 Ingraham, N R., Jr Congenital Syphilis, Diagnosis by Means of Darkfield Examination of Scrapings from the Umbilical Vein J.A.M.A., 105 560, 1935
  - 25 Ingraham, N R., Jr, Shaffer, B, Spence, B E. and Gordon, J H The Adequate Diagnosis of Infantile Congenital Syphilis Arch Dermat. & Syph., 43 323, 1941

## PREGNANCY IN DIABETES

ROSS B WILSON, M.D \*

PREGNANCY in diabetic patients has in the past caused great concern because of the complications innate in all diabetic patients plus the added hazards due to or accentuated by pregnancy. In the preinsulin era the mortality among pregnant diabetics was unquestionably higher than the average. The advent of insulin has reduced this mortality and solved some but by no means all of the problems encountered in the management of pregnant diabetic patients. Complications still attend simple diabetes and these plus the common hazards of pregnancy and childbirth result in an exacerbation or increased frequency of accidents.

### MATERNAL ASPECTS

It is not the purpose of this paper to enter into a detailed discussion of the management of diabetes per se, but to discuss some of the problems peculiar to the pregnant diabetic. It is generally conceded that in pregnancy standardization of the diabetic condition is more difficult than in uncomplicated diabetes. The fluctuation of blood sugar levels in the different phases of gestation as a result of metabolic changes incident to pregnancy and the probable effect of the fetal pancreatic secretion are well recognized in earlier writings. As a result of the many factors involved it is far more imperative that the pregnant diabetic patient have more rigid supervision by a physician capably trained in the treatment of diabetes than a nonpregnant diabetic. Close correlation of the medical and obstetrical care of these patients must be emphasized.

Fluctuation of the blood sugar levels and the varying insulin and carbohydrate requirements in the different phases of pregnancy have been pointed out. There is reason to doubt that the fetal pancreas plays a significant role in this occurrence. Frequent laboratory studies, especially urinalysis and blood sugar determination, are imperative. Urinalysis and adjustment of insulin dosage by the patient are not sufficient. Suffice to say, that the medical management of the pregnant diabetic be such that by diet regulation and if necessary insulin administration there is maintained a carbohydrate intake adequate for the pregnancy and at the same time one that maintains a blood sugar level that approximates the normal and does not create a demand on the fetal pancreas to make up a deficiency on the part of the maternal pancreatic function.

\* Instructor in Obstetrics, Jefferson Medical College; Chief, Obstetric Service, Lankenau Hospital; Obstetrician and Gynecologist, Philadelphia Lying In Hospital.

It is Allen's opinion that since the introduction of insulin the maternal mortality in pregnant diabetics has been lowered to the average of that in pregnancy uncomplicated by diabetes. At the Philadelphia Lying-In Hospital only one maternal death occurred in a total of forty-one deliveries (since 1938) in patients with diabetes. This death took place in a patient, Para VIII, as a result of a rupture of the uterus during the delivery of a breech presentation after a labor of nine hours and forty-three minutes. The infant weighed 9 pounds 6¾ ounces. There had been adequate control of her diabetic condition during this pregnancy and the maternal death was not attributed in any way to the diabetes. Considering the problem from a maternal point of view, numerous investigators have however indicated an increased incidence of *toxemia* in pregnant diabetic patients and a tendency to the production of large babies, suggesting, at least, the likelihood of difficulties due to dystocia as a result of disproportion. In the cases reviewed since 1938 at the Philadelphia Lying-In Hospital, eighteen of the forty-one deliveries resulted in babies whose weight was 8 pounds or over. There was maternal toxemia in thirteen of this group. Miller and co-workers<sup>2</sup> found that a birth weight of 11 pounds or more was eighty times as frequent in infants of diabetics as in infants of nondiabetic women. Bill and Posey<sup>3</sup> found that nine infants out of forty-four born to diabetic patients weighed 9 pounds or over. In a series of thirty-one pregnancies occurring in twenty-three diabetic patients reviewed by Lavieter<sup>4</sup> and co-workers, maternal toxemia was present in ten. There were four cases of hypertensive disease and six of preeclampsia. Bill and Posey<sup>3</sup> found twelve cases of preeclampsia in forty-four diabetic pregnant women. Allen<sup>1</sup> estimated that approximately 70 per cent of a series of patients studied by him had one or all of the cardinal signs of toxemia. Priscilla White<sup>5</sup> likewise found a high percentage of maternal toxemia in patients studied by her.

Conceding the tendency of increased incidence of toxemia in diabetes of pregnancy, the question presents itself as to why this occurs and how best it can be prevented. It is doubtful whether it can be completely clarified until the entire problem of toxemia in pregnancy is solved. At the present time, the incidence of toxemia of pregnancy in the nondiabetic has been lowered by rigid prenatal supervision entailing dietary and fluid balance and elimination regulation. However, toxemias still occur. White<sup>5</sup> has produced evidence to support the idea that in diabetic patients at least the toxemia is due to hormonal disturbance or imbalance. She and her co-workers studied 118 pregnant diabetic women by hormone assays for chorionic gonadotropin and pregnandiol. Of the 118 patients studied she found that forty-one had normal hormone levels. Only 2 per cent of these patients showed toxemia of pregnancy. Of the remaining patients who showed abnormal levels there were twenty-seven that were not treated by hormone therapy. Fifty-two per cent of these showed evidence of toxemia or

premature delivery. The remaining fifty-seven patients treated showed a much lower incidence of toxemia.

The problem of *dystocia* due to large babies has not been entirely solved by diabetic control or hormonal medication. Careful evaluation of fetal size by physical examination and the use of competent x-ray examination of the maternal pelvis and of the fetal skeleton, and the proper selection of method of delivery are of paramount importance in a pregnant diabetic.

#### FETAL AND NEONATAL ASPECTS

The reports from investigators in recent years have dealt largely with fetal aspects of this problem. As mentioned above, the maternal mortality has been lowered to that of the average prenatal case uncomplicated by diabetes. However, the fetal death rate has not been greatly lowered. It is still enormously high. Laviertes and associates<sup>4</sup> reported twelve fetal deaths in thirty-one deliveries. Miller and associates<sup>2</sup> stated that the fetal mortality rate was five times higher in diabetic than in normal pregnancy cases. Bill and Posey<sup>3</sup> studied forty-four diabetic patients and found that twelve of their infants were either stillborn or died soon after birth. Lawrence and Oakley<sup>6</sup> reported a study of fifty-four pregnancies in forty-four diabetic patients, the total number of babies was fifty-seven with a fetal mortality of 33 per cent. His studies indicated some relationship between fetal death rate and *proper supervision of the maternal diabetes*. He divided the supervision of the maternal diabetes into three groups, those that have none, those that have partial supervision, and those which were completely studied and supervised. A mortality of 70 per cent occurred in babies born of mothers with uncontrolled diabetes. When partial supervision was instituted, a mortality of 60 per cent occurred. In those with complete supervision it was lowered to 23 per cent. Allen,<sup>1</sup> however, reported that insulin accomplished relatively little in the lowering of fetal death rate. In the total number of forty-one deliveries at the Philadelphia Lying-In Hospital, in the series mentioned, there were five dead babies. Three of these occurred in patients that had had inadequate diabetic supervision. Two occurred in those considered adequate.

The chief causes of the high rate of fetal mortality has been generally conceded to be gigantism, causing dystocia and difficult delivery, as mentioned above, prematurity, independent of or associated with toxemia of pregnancy in the mother, intrauterine fetal death occurring most frequently in the last few weeks of pregnancy, and neonatal death associated with hyperinsulinism of the fetus.

In the preinsulin era the cause of large babies was thought to be the maternal hyperglycemia, but since today the incidence of large babies still remains high in spite of the widespread use of insulin, as has been pointed out, some other cause of this condition in the new-

born must be sought Bill and Posey<sup>3</sup> quote Snyder and Hoopes' work in which they produced overdeveloped offspring of animals by injection of prolactin as the beginning of the support of this idea White's<sup>5</sup> work definitely supports the hormonal origin of the condition

*Prematurity* has long been considered by obstetricians and pediatricians as one of the chief causes of fetal mortality Although many factors may be involved in the cause of prematurity, in the experience of the average obstetrician engaged in the care of prenatal patients it very frequently results from, or is associated with, some form of the toxemias Since there seems to be a high incidence of toxemia in diabetic patients, we should therefore expect a corresponding increase in fetal death rate due to prematurity and immaturity In forty-one cases studied by White,<sup>5</sup> in which she considered the normal gonadotropin and pregnandiol hormone assays as normal, no premature births occurred In this group there was only a 2 per cent incidence of toxemia, and the fetal mortality was 5 per cent In the abnormal levels, not treated by hormonal therapy, there was 52 per cent incidence of toxemia and premature delivery in the twenty-seven cases The fetal mortality in this group was 40 per cent In fifty-seven abnormal patients treated by hormones, prematurity occurred in 25 per cent and toxemia was definitely modified The fetal survival in this group in spite of the prematurity was 92 per cent

There are still those unexplained instances in which intrauterine fetal death occurs in late pregnancy or in the early stages of labor This seems to be most frequent in the last three or four weeks of gestation The theory that death is caused by some abnormal hormonal activity cannot be discarded It is in such instances that termination of the pregnancy by cesarean section three to four weeks before term is indicated At the Philadelphia Lying-In Hospital, in the forty-one deliveries of diabetics, five stillbirths occurred Three were attributed to intrauterine death before labor, and the remaining two were due to placenta praevia and difficulty in extracting the body at time of delivery

Neonatal deaths due to *hyperinsulinism* have occurred, but by proper management can be avoided By the administration of glucose by mouth or the parenteral route with proper laboratory studies of the blood sugar level of the infant, the danger of fetal death in these instances can be almost completely eliminated As soon as the infant has established regular feedings this danger has usually passed

#### METHOD OF DELIVERY

The method of delivery of diabetic patients has been the subject of much discussion In the preinsulin era all operative procedures in diabetic patients were wisely avoided whenever possible Cesarean section was especially hazardous Today with insulin the operative risk

in diabetics has greatly decreased and cesarean section is common. This tendency to resort to cesarean section is due no doubt to a desire to save babies that formerly died in utero during the last weeks of gestation, and because of the high incidence of large babies. Many, however, advocate vaginal deliveries as the routine method except in the presence of purely obstetrical indications for cesarean section such as disproportion and placenta praevia. Bill and Posey<sup>3</sup> reported thirty of forty-four diabetic patients were delivered vaginally, while fourteen had cesarean sections. Four of these were for causes other than those associated purely with diabetes. At the Philadelphia Lying-In Hospital nine of forty-one babies were delivered by cesarean section. Certainly, when obstetrical indication for cesarean section exists the operation should not be avoided in a well controlled diabetic.

#### SUPPORTIVE THERAPY ANALGESIA AND ANESTHESIA

During labor and delivery and during the immediate postpartum period, special care of the diabetic picture should be exercised. Too often as a result of lack of proper food and fluid intake due to loss of desire for food, or routine restriction of oral intake as a preparation for anesthesia and operation, or ill advised use of analgesics which prevent the oral administration of nourishment, a disturbance of glucose metabolism occurs. This can be avoided by the proper selection of analgesia and anesthesia and the use of a parenteral fluid, such as glucose solution and insulin, when indicated. The requirements of these different procedures are determined by frequent laboratory studies.

The choice of agents for analgesia and anesthesia is much wider when the diabetic phase is well regulated. In many instances spinal anesthesia and local infiltration have been avoided, but in our opinion, since we are able by competent medical supervision to maintain a safe balance in the metabolism of the patient, the use of local and regional anesthetics is not only permissible but definitely indicated. They result in less disturbance of oral intake and of fluid balance as a result of vomiting due to the anesthetic agent, and have been used by us without harmful results. There seems to be no contraindication to the use of caudal anesthesia, in fact, its employment seems to be definitely indicated since it can be used during the progress of labor as well as delivery, whether it be by the vaginal route or by cesarean section, and yet not interfere with the routine administration of fluid and food by the oral route, obviating, to some extent at least, the necessity for intravenous therapy. From the fetal aspect the use of a spinal, caudal or local anesthetic is desirable because they have no effect whatever upon the offspring. With their use the premature or otherwise abnormal baby has a far better chance for survival than when the usual inhalation anesthetics and analgesics are employed.



## BIBLIOGRAPHY

- 1 Allen, Edward J Obst & Gynec, 38 982-992 (Dec ) 1939
- 2 Miller, H C et al A M A., 124 271-275 (Jan 29) 1944
- 3 Bill, A H and Posey, F M., Jr Am J Obst & Gynec., 48 405-408 (Sept.) 1944
- 4 Lavietes, P H et al Yale J Biol & Med, 16 151-166 (Dec.) 1943
- 5 White, Priscilla J Clin Endocrinol, 3 500-511 (Sept) 1943
- 6 Lawrence and Oakley Quart. J Med, 11 45-75 (Jan) 1942

## PUERPERAL INFECTION, ITS PREVENTION AND TREATMENT

MAHLON C. HINEBAUGH, JR., M.D.\*

THE development of specific chemotherapeutic agents and antibiotics during the past ten years has materially changed the treatment of puerperal infection, and fortunately has brought about a decided improvement in maternal mortality. Despite the proven value of the sulfonamides, penicillin and more recently streptomycin† in combating infections generally, it must be remembered that puerperal sepsis is protean in its manifestations. It is rare to find a single causative organism. Generally we are dealing with a mixed infection in which symbiosis tends to increase the virulence. It is for this reason that treatment is frequently disappointing. Despite the shortcomings of specific therapies, they have come to be regarded as panaceas. It is well to sound a note of warning to the profession generally lest we be lulled into a false sense of security and overlook the fact that prevention transcends all other measures as the treatment for puerperal infection.

### PREVENTION

The prophylaxis against puerperal infection may be divided into (1) antepartum, (2) intrapartum and (3) postpartum care. *Antepartum* prevention should begin with the patient's first prenatal visit. In addition to an evaluation of the general state of health, careful search should be made for possible foci of infection and adequate treatment for their removal instituted. Detailed instruction should be given in the matter of local cleanliness, tub baths and sexual intercourse are strictly forbidden during the latter months. In addition to supervision of the diet to insure good nutrition, secondary anemia should be combated by the use of iron, vitamin B, and liver extract. These measures are designed to maintain a high standard of general health in preparation for labor.

*Intrapartum Care*—Upon admission, unless delivery is imminent, the patient should be given a shower or sponge bath before admission to the labor room. Strict care should be exercised in preparation of the

\*Diplomate, American Board of Obstetrics and Gynecology. Demonstrator of Obstetrics, Jefferson Medical College. Assistant Obstetrician, Jefferson Medical College Hospital, Philadelphia.

†This new antibiotic is at the present time under clinical investigation. It holds promise of being a specific in the treatment of infections caused by certain gram-negative bacteria, notably *Endamoeba coli*, *Eberthella typhosa*, and *Friedlander's bacillus*. To date, we have employed it in only one case. Further trial will be necessary in order to determine its value in the treatment of puerperal infection.

genitalia to avoid contamination of the vagina. This is especially true in multipara in whom the vulva gapes. It is advisable to give a cleansing enema if sufficient time permits in order to prevent contamination with feces during the delivery. If membranes have prematurely ruptured 1 ounce of a suitable antiseptic, such as zephiran chloride 1:1000, should be instilled into the vagina every four to six hours. In order to determine the progress of labor, rectal examinations are to be preferred. It must be emphasized that these should not be carried out indiscriminately. Vaginal examination should be reserved for a definite indication. Careful preparation of the patient and the obstetrician must precede their performance.

The delivery should be conducted under the most rigid aseptic technic. Meddlesome interference as by manual dilatation of the cervix, premature application of forceps or elective internal podalic version is to be condemned and serves only to increase the danger of infection. On the other hand, prophylactic forceps combined with episiotomy are advantageous and are much safer than permitting a head to pound for hours against a rigid perineum. If it becomes necessary to enter the uterus, extreme caution is urged and the examining hand should be liberally washed with a suitable antiseptic solution to prevent carrying infective organisms from the vulva or rectum into the uterine cavity. Also, following any *intrauterine manipulation* the uterus should be thoroughly explored for possible rupture. The third stage of labor should be allowed to proceed normally. Undue haste in the removal of the placenta predisposes to hemorrhage, lowered resistance and subsequent infection. Manual removal of the placenta should be restricted to those cases in which either hemorrhage, retention or adherence is endangering the patient's life and welfare. The placenta should be carefully inspected in order to make certain it has been completely expelled. The retention of even a small fragment may result in serious infection. Lacerations of the cervix, vagina, pelvic floor and perineum should be immediately repaired under proper surgical technic.

*Postpartum* prophylaxis is essentially dependent upon the strict observance of a high standard of nursing care. As soon as the patient has reacted from her labor and delivery she should be placed in the White position (commonly called Fowler). This affords freedom for lochial discharge. The use of one of the ergot derivatives is advised in order to maintain a firmly contracted uterus, thus keeping the uterine sinuses closed. Distention of the bladder should be prevented. In addition to the danger of urinary tract infection and its possible extension to the genital tract, there is mechanical interference with uterine discharge. If at any time during the puerperal period a patient becomes febrile, immediate isolation should be carried out. The need for adequate isolation facilities in any well organized maternity cannot be emphasized too strongly. These should include labor and de-

livery rooms for the potentially or actually infected case, and a well ventilated ward for their puerperal care. The staff in attendance must be completely separated from contact with clean cases

### TREATMENT

Any discussion of the active treatment of infection once established is dependent upon a knowledge of the pathology. To state it simply, the pathology of puerperal infection is that of wound infection generally. The parturient canal is always a wound surface whose extent is dependent upon the following factors: (1) the placental site and endometrial surface, (2) lacerations of the uterine body and cervix, (3)

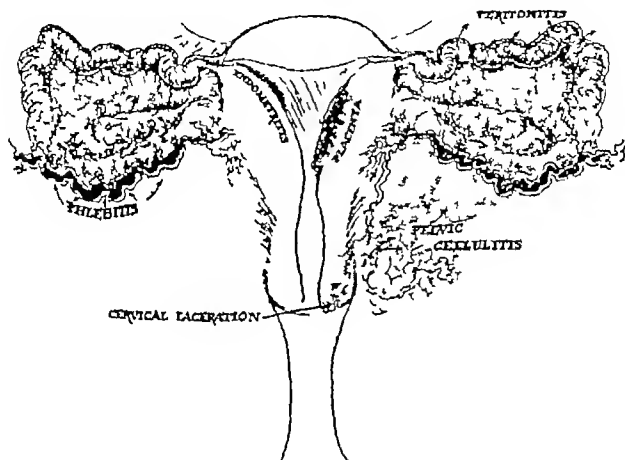


Fig 185—Areas of extension of puerperal infection.

contusions or lacerations of the vaginal vault, vulva or perineum. Fortunately the infection remains local in the majority of cases. Extension occurs by way of the lymphatics (primarily), the venous system, continuity of surfaces or by a combination of all. The accompanying diagrammatic sketch (Fig 185) serves to illustrate these routes of extension.

Although the therapeutic measures instituted in the management of puerperal infection will be separated into the various clinical types, it must not be overlooked that such simplification does not always exist clinically and frequently a combination is present.

**Vulvitis and Vaginitis.**—These types of infection most commonly occur as a result of a break in technic during the repair of an episiot-

omy or perineal laceration and is characterized by local pain, edema and redness

Treatment for this condition consists in immediate removal of sutures to afford adequate drainage and local application of heat in the form of moist sulfanilamide compresses. The external genitalia should be frequently bathed with a mild antiseptic solution, but intravaginal douches are expressly contraindicated because of the danger of carrying infection higher up. Prompt recognition and early institution of the above named measures will bring about an early subsidence of the infection and is the best means of preventing extension.

**Endometritis (Sapremia)**—Endometritis occurs more frequently than any other type of puerperal infection. Indeed, it is doubtful if infection exists without some involvement of the endometrial surface. Fortunately in most instances it remains a localized process. It usually starts about the third or fourth day postpartum, is characterized by malaise, fever, pain referable to the uterus, subinvolution and a profuse foul lochia. Formerly the diagnosis was based purely on the clinical symptoms and signs and treatment was essentially symptomatic. The patient was placed in a semisitting position, a soft diet was given, fluid intake was increased and elimination was maintained by mild laxatives or simple enemas. In an attempt to maintain a firmly contracted uterus an ice bag was placed on the abdomen and ergot derivatives were administered. Under this regimen infection usually subsided in a week to ten days with complete recovery.

The present method of treatment is dependent upon a bacteriologic diagnosis in addition to the clinical findings. This may be determined by lochial or uterine culture. The technic is as follows:

The patient is placed on a bed pan and the external genitalia are carefully cleansed with lysol solution or other suitable antiseptic. Using sterile gloves and instruments the physician gently inserts a bivalve speculum into the vagina, exposing the cervix. All lochial discharge is wiped away from the exposed cervix and vaginal fornices. A sterile glass pipette with suction bulb attached is then carried into the uterine cavity, care being taken not to allow the pipette to brush the vaginal mucous membrane, thus causing contamination. The material thus obtained is immediately cultured for both aerobes and anaerobes. The value of anaerobic culture cannot be emphasized too strongly for the anaerobic streptococcus is frequently found as a causative agent and the recovery of *Clostridium welchii* is by no means rare. A laboratory report is requested at the end of twenty-four hours to avoid delay in the institution of treatment.

The plan of specific therapy is dependent upon the type and number of organisms recovered in the culture. Of these, *Streptococcus pyogenes* is most common. Penicillin is the best therapeutic agent when infection is due to the staphylococcus, *Streptococcus pyogenes*, *Streptococcus haemolyticus*, *Streptococcus anaerobius*, gonococcus and *Clostridium welchii*. The dosage and method of administration are dependent upon the type and severity of the infection. The pri-

major object in every case is to bring the infection under control as quickly as possible. The plan adopted in our clinic is as follows. Injections are given intramuscularly, the initial dose being 20,000 units. Subsequent doses of 10,000 units each are administered every three hours making a total of 90,000 units during each twenty-four hour period. Treatment is continued until the temperature has remained normal for forty-eight hours. The penicillin is then stopped and the patient's subsequent course carefully followed. In all infections caused by the *Streptococcus hemolyticus* the initial injection is given intravenously.

Penicillin is contraindicated because it is ineffective if infection is due to *E. coli*, *B. proteus*, *B. pyocyaneus* or Friedländer's bacillus. In all cases in which infection is due to these gram-negative bacteria sulfonamides are used. We have found sulfadiazine to be most effective and it is generally well tolerated by the patient. It is administered orally, the initial dose being 2 gm followed by 1 gm every four hours. The drug is discontinued after the temperature has returned to normal. An alkali, such as sodium bicarbonate, grains 15, is administered with each dose of sulfadiazine. Blood levels of 8 to 12 mg are suggested for optimum results. These determinations are advised every forty-eight hours. Frequent blood counts should be made in view of the tendency of the drug to cause anemia and leukopenia. The urine is examined daily for the appearance of sulfadiazine crystals or any evidence of renal damage. Should this or any other toxic manifestation occur during the course of treatment the drug is stopped immediately.

Of no less importance than the specific measures discussed in the preceding paragraphs are the prevention and intensive treatment of secondary anemia. Although no arbitrary rule can be made, we routinely transfuse all patients whose hemoglobin is below 70 per cent and erythrocytes less than 3,500,000. Generally repeated small transfusions (250 cc. of whole citrated blood every second day) are more effective than one or two large transfusions. In addition, the patient is given large amounts of vitamin B complex, vitamin C, liver extract and iron.

A comparison of the results obtained with the older and the present methods of treatment leaves no doubt as to the superiority of the latter. In our experience the response has been prompt and in many instances dramatic. The patient's temperature generally returns to normal within forty-eight to seventy-two hours and all local signs of infection have disappeared. In addition to the proven value of specific therapy in combating endometritis, it has in our opinion greatly reduced the incidence of extension to the parametrium and peritoneal cavity.

**Metritis.**—Deep penetration of the uterus is most frequently seen when the causative agent, notably the hemolytic streptococcus or staphylococcus, is virulent and rapidly invasive, thus preventing the

formation of the defensive barrier which normally limits the infection to the endometrium. Clinically the differentiation between this infection and endometritis is often difficult. In some cases the symptoms and signs are the same, more commonly however, it manifests itself by increased intoxication, pain of greater severity and marked uterine tenderness. The lochia is essentially normal in quantity and there is no foul odor.

The management of this type of infection is essentially the same as for endometritis. As previously stated, the organisms most frequently encountered are the hemolytic streptococcus and the staphylococcus against which penicillin is particularly effective. An initial dose of 20,000 units is administered intravenously followed by 10,000 units intramuscularly every two hours or a total of 130,000 units during each twenty-four hours.

**Pelvic Cellulitis (Parametritis)**—Cellulitis is a not uncommon puerperal infection. In the majority of instances involvement is unilateral and is the result of invasion of the loose pelvic areolar tissue following lacerations of the cervix or lower uterine segment. In a certain percentage of cases the infection is secondary to endometritis and is caused by extension through the lymphatics of the broad ligaments. It usually starts at the base of the broad ligament and follows the planes of cleavage of the pelvic connective tissue. The inflammatory reaction is usually intense and early exudation occurs with the formation of a palpable mass. The location of the "tumor" is largely dependent upon the degree of involvement and the course which the exudate follows. Von Rosthorn has given us a useful classification of pelvic exudates based upon their origin and course of extension: (1) lateral horizontal exudates located in the base of the broad ligaments which spread to the bony pelvic wall and then anteriorly pointing above Poupert's ligament, (2) secondary extension from a previous endometritis through the lymphatics of the uterus (these exudates occur in the upper portion of the broad ligament near the uterine cornu and extend into the iliac fossae), (3) posterior exudates arising from the retrocervical tissues which extend into the rectovaginal septum, (4) anterior exudates arising from the precervical tissue which spread upward around the ureters to the abdominal wall.

Early diagnosis is difficult. Suspicion is aroused by pain and tenderness in either or both sides of the uterus without evidence of peritoneal involvement. Once tumor formation has occurred the diagnosis is easy. Without treatment one of two things may occur: (1) complete absorption without suppuration and (2) suppuration with subsequent abscess formation. When an abscess forms it may rupture spontaneously into a hollow viscus, the general peritoneal cavity, or externally through the skin, thus bringing about spontaneous cure. In a small percentage of cases the abscess becomes encapsulated, gradually shrinks in size but may remain for a period of years.

The treatment of pelvic cellulitis is directed toward limitation or extension of the process and the prevention of abscess formation. In addition to the routine measures which are carried out in all types of puerperal infection, the following plan has been adopted. At the earliest sign of infection a cervical culture is made in the hope of determining the causative organism. In most instances it is found to be *Streptococcus pyogenes*. Penicillin therapy is immediately instituted. If the infection is of moderate severity the dosage and administration is the same as that for the treatment of metritis. If on the other hand the degree of intoxication is profound, an initial dose of 20,000 units is administered intravenously, followed by constant intravenous injection of penicillin in normal saline. The drip is so regulated that 3000 units are delivered every hour. If the causative agent is found to be penicillin resistant, sulfadiazine is given. In order to establish a satisfactory blood level rapidly 5 gm. of the sodium salt is injected slowly intravenously, this is followed by the oral administration of 1 gm. every three or four hours. In cases in which the infection is of a mixed type a combination of penicillin and sulfadiazine may be used. The patient is carefully observed for any evidence of abscess formation. Should this occur an attitude of watchful waiting is adopted.

Interference is contraindicated until localization has taken place and the abscess has become completely walled off. Surgical treatment consists of incision and drainage of the abscess. The site of incision is dependent upon its location. If the abscess points above Poupart's ligament, a small incision is made just above and parallel to the ligament carefully dissecting each layer until the wall of the abscess is reached. A small opening is then made into the abscess cavity sufficient to permit its exploration by the finger to determine the extent of the abscess. The pus is evacuated and a drainage tube inserted. Great care must be exercised to avoid opening into the peritoneal cavity. A generalized and even fatal peritonitis might easily result from such a breach of technic. Whenever possible, abscesses should be drained through the vagina. Posterior abscesses are drained by simple incision into the rectovaginal septum. In some instances it is possible to drain lateral abscesses in this manner. This may be attempted if the lower limit of the abscess is at a level with the cervix. Incision is made posteriorly as near the midline as possible in order to avoid damage to either the ureter or uterine vessels. In the case of abdominal abscesses drainage is accomplished suprapubically. Following incision and drainage, healing takes place rapidly and prompt recovery is the rule.

We have found the use of x-ray of definite value in the treatment of this condition and employ it as an adjunct to specific therapy and surgery. Although the exact mode of beneficial effect is not known, it has in our experience materially helped to limit and subsequently localize the infection. It also tends to hasten healing following incision.



and drainage. Small doses are used, 25 to 75 roentgens per treatment, the total dose not to exceed 500 roentgens.

**Pelvic Peritonitis (Perimetritis)**—Invasion of the perimetrium may occur secondary to many forms of local puerperal infection such as endometritis, pelvic cellulitis or a previously existing salpingitis. Fortunately in most cases the invading organisms do not possess a high degree of virulence and the infection remains limited to the pelvic peritoneum. Extension to the peritoneal cavity takes place (1) through the lymphatics of the uterus, (2) the blood vessels, (3) a combination of both, (4) rupture of an old pyosalpinx during labor and (5) by direct invasion following rupture or laceration of the upper uterine segment. The pathologic findings in puerperal peritonitis are identical with those of surgical peritonitis. The symptoms and signs vary with the mode in which infection reaches the peritoneum. Extension through the lymphatics from a previous endometritis is the most common, in which case the onset is gradual and early recognition difficult. In contrast, peritonitis which follows a ruptured pyosalpinx is abrupt in onset and is accompanied by severe pain, marked tenderness which rapidly spreads over the abdomen, and collapse. We have seen three fulminating cases of peritonitis following this accident during spontaneous delivery. In each instance the infection was so overwhelming that the patient succumbed within seventy-two hours. The diagnosis of the cause was made at autopsy.

Before the days of specific therapy the end result of treatment was at best unsatisfactory. Under the present plan of management the patient is placed in Fowler position. This affords postural drainage and tends to prevent ascension of the infection. Vomiting is controlled and decompression accomplished by either the Wangenstein apparatus or a Miller-Abbott tube. The passage of gas per rectum is facilitated by the insertion of a rectal tube. Enemas should not be given. Fluid intake is maintained by intravenous drip, 1500 to 3000 cc daily of 5 per cent glucose in normal saline. Blood transfusions are routinely administered to combat anemia and increase the patient's resistance. The predominant organisms which cause puerperal peritonitis are susceptible to penicillin. It is administered by the intravenous route previously described under the treatment of severe pelvic cellulitis. Because of the severity of the infection the dosage requirement is higher. In addition to the 20,000 unit initial dose, the intravenous drip is regulated to deliver 5000 units during each hour. Sulfadiazine may be used in conjunction with penicillin because of the inhibiting effect on the colon bacillus which is frequently found as a secondary invader. The dosage and method of administration have been previously described.

If the infection responds well to treatment, early resolution and absorption may be expected. In certain instances, however, suppuration with subsequent abscess formation develops. When this occurs, incision and drainage of the abscess cavity is indicated. As in the case

of pelvic cellulitis, surgical interference is delayed until the abscess cavity has become walled off. Most commonly the collection may be found in the cul-de-sac, the operation for which is posterior colpotomy. The removal of infected tubes or ovaries should be delayed until after all evidence of acute infection has completely subsided. Failure to observe this precaution might readily be followed by a rapidly spreading or fatal generalized peritonitis.

X-ray therapy has proved to be of definite value in the treatment of these cases. The dosage is exactly the same as for pelvic cellulitis.

**Bacteremia (Septicemia)**—Bacteremia is the most serious type of infection which occurs during the puerperium. Prior to the development of specific therapy the death rate from this dreaded disease was extremely high and on a par with hemorrhage and toxemia. The most important single causative agent is the beta hemolytic streptococcus but the staphylococcus, anaerobic streptococcus and many other organisms may be found. Direct involvement of the blood stream may be gained by the lymphatics (most frequent), by the blood vessels or a combination of the two. The resultant clinical picture is largely dependent upon the mode of invasion and the virulence of the infecting microorganisms. A period of incubation which is somewhat variable precedes the actual outbreak of symptoms. During this time there may be evidence of the local infection from which the bacteria enter the blood stream. It is generally impossible to determine the exact time of invasion. Following this period of incubation, the characteristic syndrome of a serious bacteremia appears. There is a severe shaking chill lasting from five to thirty minutes during which the temperature rapidly rises and reaches  $103^{\circ}$  to  $104^{\circ}$  F. The pulse rate is increased out of proportion to the elevation of temperature. In addition there are the usual symptoms of profound intoxication and signs which point to extension of infection from its site of origin. The diagnosis is confirmed by positive blood culture. Early in the course of the disease there may be an insufficient number of bacteria in the blood stream to obtain a positive culture. Under such circumstances a clinical diagnosis must be relied upon. The organisms are most frequently recovered from the blood during the rigor when the temperature is rising and should be taken at this time. Cultures made after the chill has subsided and the temperature is receding are of little value. It is sometimes necessary to make repeated cultures before a positive one is obtained. In addition to the isolation of the causative micro-organism the determination of the number of colonies per cubic centimeter of blood is of considerable prognostic value.

At the present time treatment for puerperal bacteremia is largely preventive. When early recognition and active treatment of local infection is properly carried out, blood stream infections will almost invariably be prevented. Penicillin is by far the best therapeutic agent and should be given intravenously. The dosage and administration have

been previously described under the treatment of peritonitis. We believe that repeated small blood transfusions are equally as important as specific therapy.

**Pyemia (Metastatic Bacteremia).**—Pyemia is a term used to describe a more chronic form of septic infection. It is usually secondary to local uterine infection in which venous thrombosis has occurred. Small pieces of infected thrombi break loose to form emboli which are carried through the blood stream to distant parts, thus causing metastatic pus formation. The treatment for this condition combines the specific measures employed in bacteremia, and the incision and drainage of local abscesses which form.

**Thrombophlebitis.**—Infection of the veins with thrombus formation may occur as the result of severe trauma during delivery or in association with local infection. Frequently the infection begins in the uterus as a local thrombophlebitis, then extends by way of the pelvic veins through the common iliacs either upward into the vena cava or downward through the external iliac into the femoral veins. The infection is of two types, suppurative and nonsuppurative. In the suppurative form embolic phenomena are characteristic, closely resembling pyemia. The best example of the nonsuppurative variety is femoral thrombophlebitis (*phlegmasia alba dolens*). The diagnosis of pelvic thrombophlebitis is extremely difficult. After several days of apparent normalcy the patient becomes febrile and complains of pelvic pain. Examination fails to reveal any evidence of local disease. Fortunately in the majority of cases the infection is limited and of the nonsuppurative type. Spontaneous recovery is the rule. For the most part, suppurative thrombophlebitis occurs in conjunction with endometritis, pelvic cellulitis, etc. Specific therapy has already been instituted to combat the primary infection and is the best means of prevention against resultant embolism.

Femoral thrombophlebitis was formerly treated by complete rest of the affected leg, elevation to an angle of 30 degrees and a firm supportive bandage to limit swelling. Hot moist packs were also used in the hope of preventing chronic venous congestion. Under this regimen the infection usually subsided in anywhere from ten to sixteen days. Several years ago this method of treatment was supplanted by paravertebral nerve block. The rationale for this plan is based upon the concept that vasospasm which results from afferent impulses arising in the injured vein segment was primarily responsible for the development of thrombophlebitis. When this procedure was carried out the relief of pain was prompt and the disappearance of edema rapid. Thus the duration of the infection was materially shortened. Heparin has also been used with considerable success. The use of this drug, however, is not without danger. At the present time we advocate *continuous caudal or continuous spinal anesthesia*. In our opinion its superiority over paravertebral nerve block is due to the marked vasodilatation

which occurs and is maintained for the duration of the anesthesia. Most recently we have employed continuous spinal, using 1.5 per cent metycaine. One cubic centimeter or 15 mg is given at intervals of forty minutes. The duration varies with the severity of the infection. In our series, which up to the present time is small, the shortest period of time has been four hours and the longest twelve hours. Relief of pain is immediate, and usually within five to ten minutes vasodilatation of the extremities is manifested by marked warmth and redness. In most instances edema disappears within twenty-four hours, the temperature returns to normal and the patient is allowed out of bed at the end of seventy-two hours. Further trial will of course be necessary in order to properly evaluate this plan of treatment.

**Infected Abortion**—The treatment of this serious and often fatal infection has been reserved for discussion separately, because up to the present time there is considerable controversy as to the best method of management. On the one hand we have a group of conservatives who insist that a "hands off" policy is the only safe course, while on the other hand a second group equally as sincere maintains that active interference gives the best results.

Under the conservative plan the treatment is directed toward the infection with complete disregard for the retained products of conception. In addition to routine supportive measures for any puerperal infection, penicillin or a sulfonamide is given. The dosage and method of administration is dependent upon the severity of the infection and do not differ in any way from the plans previously described in the treatment of endometritis, pelvis cellulitis, and so forth. Only after all acute features of the infection have subsided and the temperature has remained normal for several days is it deemed safe to empty the uterus. This is accomplished by simple evacuation and blunt curettage. This rule of "stay out of the uterus" while active infection is present may be disregarded only in cases of severe hemorrhage which may necessitate the removal of secundaries protruding through the cervical canal or the insertion of a vaginal pack.

The radical plan of management is based upon the concept that the unexpelled products of conception rapidly become necrotic and as such are a fertile field for the growth and multiplication of pathogenic bacteria. Such a concept is at least partially substantiated by the fact that spontaneous expulsion of the retained products of conception is in the vast majority of cases promptly followed by recovery. In our clinic the radical plan was adopted three years ago and up to the present time results have been most gratifying.

The method is as follows: Upon admission, a cervical culture is immediately taken (using the technic described under Endometritis) and a twenty-four hour report is requested. Sulfadiazine therapy is immediately instituted, giving an initial dose of 2 gm followed by 1 gm. every four hours. The general condition of the patient is deter-

mined by thorough physical examination, complete blood count, blood sedimentation and urine analysis in order to evaluate the operative risk. If the patient's general condition is satisfactory, preparation for operation is made. The final decision is dependent upon the laboratory report. If the *Streptococcus hemolyticus* is recovered, surgical interference is definitely contraindicated and the conservative plan is followed, otherwise the patient is removed to the operating room regardless of fever and the uterine contents are completely evacuated. The uterus is then firmly packed with either sulfanilamide or iodoform gauze which is to be removed in twenty-four hours. Depending upon the organism recovered from the cervical culture, sulfadiazine may be continued or penicillin therapy instituted. Usually at the end of forty-eight hours the patient's temperature has returned to normal and she is able to get out of bed.

In our opinion the so-called radical plan possesses definite advantages over conservative management, to wit (1) recovery is much more rapid, (2) the length of hospitalization is materially reduced, and (3) the end result is equally as good.

#### BIBLIOGRAPHY

- 1 De Lee, J B and Greenhill, J P. *The Principles and Practice of Obstetrics* Philadelphia, W B Saunders Co, 1943
- 2 Adair, F L. *Obstetrics and Gynecology* Philadelphia, Lea & Febiger, 1940
- 3 Keefer, C S, Blake, F G, Marshall, E. K., Jr, Lockwood, J S and Wood, W B., Jr. *Penicillin in the Treatment of Infections, a Report of 500 Cases* J.A.M.A., 122 1217-1224 (Aug 28) 1943
- 4 Herrell, W E. *Penicillin and Other Antibiotic Agents* Philadelphia, W B Saunders Co, 1945
- 5 Novak, E. *Gynecological and Obstetrical Pathology* Philadelphia, W B Saunders Co, 1941
- 6 Waksman, S A. *Microbic Antagonisms and Antibiotic Substances* New York, The Commonwealth Fund, 1945
- 7 Studdiford, W E. *Observations on Hemolytic Streptococcus Infections Following Delivery and Abortion Since the Advent of Sulfanilamide* Am J Obst & Gynec., 43 619, 1942
- 8 Curtis, A H. *Obstetrics and Gynecology* Philadelphia, W B Saunders Co., 1933
- 9 Swenson, P. Personal communication

## VACCINATION DURING PREGNANCY AS A PROPHYLAXIS AGAINST PUERPERAL INFECTIONS

J BERNARD BERNSTINE, M D , F.A.C.S \*

THE problem of immunity to puerperal sepsis has attracted the attention of clinicians and biologists ever since the bacterial origin of infection has been recognized. In 1923 and 1925 Dick and Dick inaugurated a cutaneous test for the toxin of scarlet fever. Later, this test was extended to the field of obstetrics and patients were examined for susceptibility by the Dick method. These investigations added much to the knowledge of immunity to certain strains of the streptococcus and have emphasized the importance of the natural resistant agents of the body in combating and eradicating infection.

The problem in puerperal sepsis, however, goes beyond the question of streptococcic infection alone. While the most severe of the blood infections are generally due to hemolytic strains, many other morbid lesions are produced by bacilli of the colon group and various other cocci. With these facts in mind we have undertaken to culture the types of organisms commonly found in puerperal infection, test their effect upon laboratory animals, and by means of a vaccine made from the cultures, endeavor to elevate the immunity of the pregnant woman to puerperal infection in general.

The content of this paper has to do with the technic of preparation, the experimental trials in mice, and the results obtained by the use of the vaccine. The number of cases reported to date including the latest group totals 973 cases.

Our first problem was to study carefully the bacteriology of the birth canal, especially the cervix and endocervix of pregnant women. The bacterial strains employed in the vaccine used in this study were obtained from the patients (pregnant women) attending the antenatal clinic of the Philadelphia General Hospital. The cases studied were picked at random and not selected, the only requirements being that the patient employed should have had no sexual intercourse for at least twenty-four hours preceding the taking of the cultures, and she must not have taken a vaginal douche.

The patient thus employed was placed in the dorsal position, and a dry, sterile bivalve vaginal speculum was introduced into the vagina. The other hand, still being uncontaminated, was employed in obtain-

---

From the Department of Obstetrics, Jefferson Medical College Hospital, Philadelphia.

Associate Professor of Obstetrics, Jefferson Medical College. Attending Obstetrician, Jefferson Medical College Hospital.

ing the cultures. The first was taken from the cervix with a sterile cotton swab, and the assistant immediately placed this specimen in a sterile tube containing blood agar, solidified, to prevent its drying. The second specimen was taken from the endocervix, and treated likewise. All specimens were taken to the laboratory and subcultured within thirty minutes from the time they were obtained.

### CULTURAL MEDIA AND METHODS

For the purpose of isolation and identification of organisms, we employed 5 per cent defibrinated horse blood agar plates and slants, beef infusion broth, pH 7.6, and plain 2.5 per cent infusion agar plates and slants. In the case of gram-negative bacilli, their identification was made certain by their carbohydrate fermentation reactions.

Each of the two specimens was streaked to each of two blood agar plates and then the swabs were placed separately in test tubes containing 5 cc of beef infusion broth. One of the blood agar plates from each specimen was incubated under partial oxygen tension, the two remaining plate cultures being kept at normal aerobiosis. The reduced oxygen tension was obtained by placing the cultures in Novy jars and partially evacuating the air by means of a Cenco-Hyvac pump. All cultures were then incubated for twenty-four hours at 37.5° C., when they were examined for growth, grossly and microscopically. The broth cultures were subcultured to blood tension for twenty-four hours or longer. No culture was considered negative for growth until after an incubation period of at least seventy-two hours. No direct smears from patients were made, since we were interested only in bacterial growth. However, routine smear preparations are studied on all patients in this clinic for evidence of neisserian infection.

In the series of twenty-five cases studied we failed to recover any organisms from the cultures grown under partial oxygen tension which we did not obtain in cultures grown at normal oxygen tension. The gonococcus was conspicuous by its absence in all cultures.

The strains to be incorporated later in a vaccine were placed in pure culture on suitable media and stored at a temperature of 6° C as soon as their isolation and identification were made.

The complete bacterial flora of the series studied is shown in Table 1. We have not listed the cultural results from the cervix and endocervix separately, because we found only a slight and insignificant variation in the bacterial flora from the two sources.

### PREPARATION OF THE VACCINE

The majority of the various strains of organisms incorporated in the vaccine were pathogenic for mice. Only strains which grew smoothly in broth and produced smooth colonies as solid media were employed. All of these latter strains were grown by repeated transfer in broth for four successive days and then the growth from an eighteen-hour culture was collected in sterile physiologic saline, washed once with normal saline and standardized to 2 billion per cc by the turbidity method, using as standards of comparison suspensions of staphylococci in gelatin of a 2 billion per cc concentration. All streptococci were collected by centrifuging the eighteen-hour growth obtained from cultures in beef infusion broth, pH 7.6. The remaining strains of organisms employed in the vaccine were grown on beef infusion agar slants. The eighteen-hour growth was washed from these slants with sterile normal saline, washed once and standardized as above noted.

TABLE 1—COMPLETE BACTERIAL FLORA OF SERIES STUDIED

Patient	Age	Color	Month of Gestation	Staph. Albus	Staph. Aur	Strep. Hem.	Nonhem. Strep	Strep. Viral	B. Coll	B. Diptheroides	B. Subl.	Yeasts	Proteus	B. Faecalis Alcal.
1 O McS	26	W	5	+	+			+	+	+	+	+	+	
2 M H.	20	W	5	+										
3 E H.	23	W	5	+										
4 H C.	31	W	5	+	+									
5 F B.	27	B	4	+				+						
6 R J.	25	B	4	+										
7 M. A.	21	B	3	+										
8 E B.	21	W	6	+										
9 E S.	26	W	5	+										
10 M. L.	27	W	6	+										
11 B T.	27	B	3	+		+	+							
12 N C.	24	B	5	+					+					
13 A B.	23	W	7	+										
14 D T.	26	W	4	+										
15 C d M.	23	W	5	+										
16 C P.	23	W	6	+										
17 M R.	23	W	3	+										
18 C B.	22	B	6	+										
19 R G.	20	B	3	+										
20 W W.	22	B	6	+										
21 L. H.	20	B	4	+										
22 E. L.	19	W	8	+										
23 L. B.	28	W	5	+										
24 M S.	27	W	5	+										
25 E R.	28	W	5	+										
Totals				22	2	1	4	11	2	20	4	4	1	1
Per cent				88	8	4	16	44	8	80	16	16	4	4

\* Colonies hemolyzed blood agar



Each of the separately collected vaccines was subcultured to blood agar to rule out contamination. The vaccines were then killed by the addition of sufficient 5 per cent alcoholic solution of thymol to make a concentration of 0.4 per cent thymol, and were stored at 6° C overnight. On the following day each of the vaccines was diluted with an equal volume of sterile normal saline thus giving a concentration of 1 billion per cc. These diluted vaccines were placed in sterile 60 cc vaccine bottles and tested for sterility by subculturing to blood agar slants, the latter being incubated aerobically and anaerobically for forty-eight hours. The bottles were then stoppered with appropriate rubber stoppers, the latter being sealed by the application of collodion. These vaccines were then properly labeled and stored continuously at 6° C as stock suspensions of killed single type organisms from which a mixed vaccine could readily be made. The accompanying outline summarizes the types of vaccines employed in the final mixed vaccine used in our studies (Table 2).

TABLE 2—COMPOSITION OF THE MIXED VACCINE

	No. of Strains	Proportion, Per Cent
1. <i>Streptococcus hemolyticus</i>	5*	35
2. <i>Streptococcus viridans</i>	8	15
3. <i>Staphylococcus aureus</i>	2	25
4. <i>Bacillus coli communis</i>	2	15
5. <i>Streptococcus nonhemolyticus</i>	4	10

\* Four of these strains were recently isolated strains, 2 were isolated from the blood, and 2 from the lochia of patients with puerperal infections.

When it was found that all of these individual vaccines were sterile, a mixed vaccine was prepared, varying the percentage content of the various strains of organisms according to the above designated proportions. The desired quantity of each individual vaccine was removed from the "stock" bottle aseptically with a Luer syringe and hypodermic needle and the six fractions were pooled in a small sterile flask. An equal volume of sterile saline was then added to the flask and after thoroughly mixing its contents, this final preparation was transferred to 30 cc vaccine bottles. These were proved sterile by subculturing and further cared for by methods above noted.

It will be noted that the last saline dilution reduced the concentration of organisms to  $\frac{1}{2}$  billion per cc., while at the same time the concentration of thymol was reduced from its original killing concentration of 0.4 per cent to a preservative concentration of 0.1 per cent. This concentration of organism and of chemical has proved satisfactory in a large series of cases observed by us. We can readily employ the necessary dosage with no demonstrable reaction attributable to the chemical preservative.

#### RESULTS OF TESTS ON ANIMALS AND NONPREGNANT WOMEN

It is considered inadvisable by some authorities to vaccinate women during pregnancy, but there was conspicuous lack of tangible evidence in the literature to substantiate this belief. However, before attempting vaccination of pregnant women, we employed the vaccine repeatedly in mice. We then vaccinated a series of nonpregnant women of child-bearing age.

Twelve mice were divided into Groups A and B of 8 and 4 mice, respectively. Two experiments were conducted simultaneously on these groups. Group A was immunized by repeated injections of the vaccine, beginning with 0.1 cc. and increasing the dose until nine injections had been given at regular intervals over a three-week period. The final dose was 1.0 cc. and all mouse injections were given intraperitoneally. Ten days after the last injection, all mice of Group A were inoculated with a lethal number of living organisms obtained from young cultures of our isolated strains, one strain each of *Streptococcus viridans* and of *Streptococcus hemolyticus* being employed. This lethal dose was determined by inoculation of a series of nonvaccinated (normal) mice, when it was found that 0.5 cc. of an eighteen-hour broth culture of streptococci was uniformly fatal in twelve hours or less. All of Group A survived, and two litters of apparently normal mice were found among these animals during the study.

Mice of Group B were subjected to single, large doses of vaccine intraperitoneally. Doses of 0.3, 0.5, 0.75, and 1.0 cc., respectively, were given. As in Group A, these mice were observed for reactions. The two mice receiving the larger injections appeared to have a moderate reaction and were sluggish for several hours following the injection, in contrast to Group A mice which showed no reactions. However, on the days following vaccination Group B mice showed no evidence of untoward reaction and were normal in appearance. There was born a normal litter to Group B also.

Following our studies on mice, ten female patients who were already hospitalized were selected for study. These women were not pregnant, but were of the childbearing period, free from acute infectious diseases and well informed of the nature of the studies we wished to make. (Some of these patients were ambulatory while others were bedridden.) Careful records were kept in which the pulse, temperature, respiratory rate, blood pressure and urinalysis were recorded. They were observed especially for evidence of local or general reactions to the injections.

All of these women were first given an intracutaneous injection on the flexor surface of the forearm of 0.05 cc. of the vaccine. Subsequent injections were given subcutaneously over the deltoid region at four-day intervals until a total of ten injections had been given each woman. The dosage was gradually increased from 0.05 cc. to 1.0 cc. at the tenth and final injection. Aside from an occasional complaint such as slight soreness at the site of injection or mild malaise, no untoward reactions were observed. Among this group of women were several postencephalitics and cases of multiple sclerosis. Though this study was obviously not therapeutic in its aim, several of this group volunteered information to the effect that they had improved and felt better following vaccination.

## VACCINATION OF PREGNANT WOMEN

The observations and results obtained by the vaccination of mice, and also of nonpregnant women of the childbearing period, were not only gratifying but encouraged us to proceed with the actual vaccination of the pregnant woman

The reports of studies were presented in four groups Group I presented in 1936 consisted of 51 vaccinated pregnant women Group II consisting of 177 similarly vaccinated cases was reported in 1939 Group III was presented in 1941 and consisted of 271 additional patients Group IV or the latest number of vaccinated cases includes 471 additional patients As was mentioned above, Groups I, II, III have been reported previously, therefore, this treatise will deal mainly with Group IV. This study (Group IV—471 patients) was conducted entirely on patients attending antenatal clinics of Jefferson Medical College Hospital. Patients were accepted for vaccination irrespective of their past or present medical or obstetric histories, their acceptance depending only upon their willingness to cooperate in this study Routine studies on these women consisted of the following complete history (medical and obstetric), physical examination, urinalysis, blood pressure and weight determination (at each weekly visit) Complete blood count and blood Wassermann and Kahn tests were performed Other studies and observations were made when the occasion demanded

This report includes the observations on 471 women in our present series during the antenatal period, labor and puerperium Additional observations were also made on the babies born to these women

## PROCEDURE OF VACCINATION

All injections were administered with a tuberculin syringe and a 25 gauge hypodermic needle The skin at the site of inoculation was first prepared by cleansing with sterile water, then sponged with 95 per cent alcohol Each patient was first given an intracutaneous injection of  $\frac{1}{2}$  minum of vaccine on the flexor surface of the forearm, and then observed for local and general reactions at from one to three day intervals Subsequent injections were given at weekly intervals, intramuscularly in the deltoid region The initial intramuscular injection was 1 minum, the second injection 2 minims, with subsequent injections as follows 4, 8, 12 and 16 minims The maximum dose was the one administered until the patient was delivered The total number of injections varied in individual cases of this present series (Group IV) from a minimum of 8 to a maximum of 30 Figure 186 illustrates the period of gestation during which the vaccine was administered It will be noted that the majority of the patients received their vaccinations from the fourth to the ninth month This corresponds with the approximate time of gestation when they registered in the outpatient obstetric department.

No. of Cases	Months							
	2	3	4	5	6	7	8	9
41								
81								
110								
117								
82								
39								
*1								

\* Abortion.

Fig 186.—Period of gestation during which the vaccine was administered.

Table 3 illustrates the number of injections received by the patients

TABLE 3—NUMBER OF INJECTIONS RECEIVED BY PATIENTS

No of Injections	No of Cases	No of Injections	No. of Cases
8	70	20	18
9	57	21	12
10	44	22	3
11	30	23	9
12	36	24	6
13	30	25	4
14	35	26	6
15	28	27	1
16	27	28	2
17	18	29	1
18	18	30	1
19	15		

Table 4 is representative of patients vaccinated as to age and gravida.

TABLE 4—AGE AND GRAVIDA OF PATIENTS VACCINATED\*

Age	No of Patients	Gravida	No of Patients
10-15	18	I.	345
16-20	222	II	61
21-25	134	III	24
26-30	52	IV	20
31-35	32	V	7
36-40	8	VI	4
41-45	5	VII	2
		VIII	5
		IX	1
		XIII	1
		XV	1

\* Included in this category were 345 primigravidae and 126 multigravidae the youngest patient was 12 years of age and a primigravida, while the oldest were 42 years of age one gravida I and the other gravida X.

Table 5 contains a list of the complications and diseases that the patients in this study had prior to the present pregnancy

TABLE 5—COMPLICATIONS AND DISEASES PRIOR TO PRESENT PREGNANCY

Complications	No of Cases	Complications	No of Cases
Diphtheria	13	Chronic tonsillitis	1
Gallbladder disease	1	Typhoid fever	7
Scarlet fever	35	Pulmonary tuberculosis	1
Epilepsy	1	Glandular tuberculosis	1
Chorea	2	Tuberculosis of spine (operation)	1
Nephritis	1	Puerperal sepsis	1
Oophorectomy	3	Pyelitis	1
Pneumonia	37	Nephrectomy	2
Peritonitis	1	Rheumatic fever	3
Abortion	4	Heart disease	1
Eclampsia	2	Hip joint disease	1
Anemia	2	Cesarean section	5
Influenza	5	Severe laceration of pelvic floor	1
Appendectomy	23	Breast abscess	1
Chronic tracheobronchitis	1	Osteomyelitis of jaw	1
Preeclampsia	2	Hay fever	1
Herniorrhaphy	1	Myomectomy	1
Cervical adenitis	1	Bronchial cyst	1
Eczema	1	Cerebrospinal meningitis	1
Chronic arthritis	1	Papilloma of bladder	1

Table 6 contains a list of complications observed during the present pregnancy in the vaccinated group

TABLE 6—COMPLICATIONS DURING PRESENT PREGNANCY

Complications	No of Cases	Complications	No of Cases
False labor	17	Nausea and vomiting	50
Lymphogranuloma venereum (plus Frei test)	1	Pernicious nausea and vomiting	3
Epilepsy	1	Nephritis	1
Scarlet fever	1	Preeclampsia	23
Appendectomy	1	Eclampsia	1
Bartholin's abscess	2	Anemia	61
Papilloma of vagina	1	Contracted pelvis	13
Trichomonas vaginalis	1	Pulmonary tuberculosis	3
Gonorrhea	1	Heart disease	11
Ovarian cystectomy	1	Severe laceration of pelvic floor	2
Tracheobronchitis	2	Pyelitis	8
Influenza	1	Polyhydramnios	3
Badly abscessed teeth	1	Obesity (over 200 lbs)	3
Banti's syndrome	1	Cardiac decompensation	3
Psoriasis	1	Placenta praevia	5
Ischiorectal abscess	1	Asthma	5
Condylomata	1	Nephrolithiasis	4
Fibroid uterus	2	Bronchiectasis	1
Whooping cough	1	Syphilis	6
Intrauterine fetal death	1	Threaten abortion	2
Incisional hernia	1		

The types of complications observed in our vaccinated group may be generally accepted as factors predisposing, either directly or indirectly, to puerperal infections. It is common knowledge that local or general complications during pregnancy often bear an important relationship to the incidence of puerperal morbidity. The group of complicated cases in this study demonstrates feasibility of vaccination with regard to tolerance in the pregnant women with abnormalities.

The delivery of these patients should be considered very carefully. We deemed it unwise for the physicians in attendance to have knowledge of the prophylactic vaccination, since it was our aim to have different men deliver these patients. This was done only to aid in obtaining results that would be impartial and unbiased.

TABLE 7

Features of Labor	No of Cases	Features of Labor	No of Cases
Episiotomy	270	Forceps (mild)	16
First degree laceration	20	Breech extraction	14
Second degree laceration	21	Cesarean section (classical)	5
Moderate postpartum bleed- ing	8	Cesarean section (low)	12
Placenta praevia	4	Ischiorectal abscess	1
Premature separation of placenta	3	Retained placenta	3
Manual removal of placenta	3	Prolapsed cord	1
Premature rupture of mem- branes	29	Short labor	4
Premature labor	11	Version	4
Prolonged labor	32	Craniotomy and embryot- omy	1
Surgical induction	10	Scanzoni's maneuver	1
Medical induction	6	Adherent placenta	2
Born before doctor arrived	2	Cardiac decompensation	1
Forceps (low)	75	Annular detachment of cer- vix	1

It is not within the scope of this paper to give in detail a description of the labor and delivery of this entire series. Table 7 illustrates the incidence of certain features of delivery which should be taken into consideration, since it is a known fact that the conduct of labor has a direct bearing on puerperal morbidity. There were 343 patients in this series who delivered themselves spontaneously and the remainder had operative interference.

#### PUERPERAL MORBIDITY

Our criteria for puerperal morbidity are based upon the accepted standard at the Jefferson Medical College Hospital, to wit, any elevation reaching 100.4° Fahrenheit on any two readings or two successive readings exclusive of the first twenty-four hours following delivery that the patient is considered morbid.

In our series of vaccinated cases, twenty patients were morbid during the puerperium, a total of 4.24 per cent, as compared with the

nonvaccinated group for the same period who showed a puerperal morbidity of 17.1 per cent

TABLE 8.—CAUSES OF PUERPERAL MORBIDITY IN VACCINATED GROUP

Cause	No of Cases
Cesarean section (operation reaction)	16*
Degeneration of uterine myoma postpartum	1
Craniotomy and embryotomy	1
Cystitis	1
Rupture of Bartholin's abscess during labor	1

\* One cesarean section not morbid.

### HOSPITALIZATION PERIOD

The patients in the vaccinated series showed a variation from a minimum of five to a maximum of thirty-three days' hospitalization (Table 9). The factors which necessitated longer hospitalization were

15 days (4 cases)

- a. Negro, age 27, gravida I, rheumatic heart disease, contracted pelvis, cesarean section
- b. White, age 17, gravida I, eclampsia, contracted pelvis, cesarean section when recovered from eclampsia
- c. Negro, age 16, gravida I, cephalopelvic disproportion, cesarean section
- d. Negro, age 25, gravida I, admitted to hospital in labor and febrile, android pelvis, deep transverse arrest of head (original R.O.P.), intrauterine fetal death, forceps delivery, delivered of macerated fetus

16 days Negro, aged 25, gravida V, cardiac disease, decompensated during pregnancy, cesarean section and sterilization

21 days (2 cases)

- a. Negro, aged 18, gravida I, severe preeclampsia, surgical induction of labor, spontaneous delivery (L.O.A.), mediolateral episiotomy, primary repair
- b. Negro, age 21, gravida I, premature separation of placenta (complete detachment of placenta), cesarean section, blood transfusions before and after operation, reaction following transfusion

33 days White, age 24, gravida I, rheumatic heart disease, mitral stenosis, mid-forceps (R.O.P.), acute cardiac decompensation, remained in hospital for cardiac condition as medical case.

TABLE 9 —HOSPITALIZATION PERIOD

Days in Hospital	No of Patients	Days in Hospital	No of Patients
5	1	12	9
6	4	13	2
7	22	14	7
8	160	15	4
9	214	16	1
10	41	21	2
11	3	33	1

Note 93.8 per cent of patients in the series remained in the hospital ten days or less, 98.3 per cent were in the hospital two weeks or less

## BABIES BORN OF VACCINATED MOTHERS

A study of these vaccinated persons would not be complete unless it included observations of the newborn. There were 251 males and 225 females, with their weights ranging from 2 pounds to 10 pounds 4 ounces (Table 10), and there were six sets of twins. In the entire

TABLE 10 —WEIGHTS OF THE NEWBORN

Weight in Pounds	Males	Females
2	0	1
3-4	3	0
4-5	2	2
5-6	32	30
6-7	75	85
7-8	86	80
8-9	42	22
9-10	11	3
10-11	0	2

group there was one abortion, which was induced, and seven stillbirths. An explanation of the stillbirths follows

1. Premature, polyhydramnios.
2. Premature, premature rupture of membranes, breech, prolapsed cord.
3. Mother a severe preeclamptic (blood pressure systolic, 270 diastolic, 210), necrotic placenta, spontaneous delivery
4. Premature.
5. Premature, one of twins (uniovular)
6. Moderately contracted pelvis, labor 74 hours, midpelvic arrest of head, for cephs delivery, macerated.
7. Craniotomy and embryotomy (macerated)

It is felt that anything which might influence puerperal morbidity or mortality or possibly decrease the incidence of puerperal infection is worthy of consideration.

F. L. Adair has stated that 90 per cent of 7380 obstetric deaths were due to sepsis. L. Colebrook is authority for the statement that the present condition is roughly thus. Casualties from infection represent nearly 50 per cent of the total deaths directly associated with child-bearing if those due to abortion are included, and, in addition, there is a large amount of serious nonfatal illness. Therefore, we believe that if anything can be employed in an attempt to increase the resistance of pregnant women to puerperal infections, it should be given consideration. It would be ridiculous to say that puerperal infections can be abolished entirely and forever; but, on the other hand, it is not impossible for such infections to be reduced to a minimum.

I would like to cite one case as an example of what may happen to a patient in labor and the possibilities that may arise and contribute towards puerperal infection.



Patient C T, 26 years old, white, gravida III, received eleven injections of vaccine during pregnancy. She went into labor at term, and delivered spontaneously a male child weighing 9 pounds. The child was born before the arrival of the doctor, and was expelled on the bathroom floor. A kind neighbor severed the umbilical cord and tied it. The doctor arrived and the placenta could not be expelled. The patient was removed to the hospital where the placenta was manually removed. She made an uneventful recovery and left the hospital in eight days and at no time was she morbid.

### ANALYSIS OF RESULTS

The first three series of cases that were presented totaled 502 vaccinated patients. In this present series we have observed an additional 471 cases, making a total of 973 vaccinated patients. As stated before, the patients were not hand picked, in reality, we hoped to obtain a representative group such as may be found in a cross section of the average obstetric practice with its associated complications, namely, primiparous and multiparous women during pregnancy, labor and the puerperium.

The vaccine was administered to pregnant women with various complications in addition to their pregnant state. These complications varied in type and severity, and yet we failed to observe a single case that presented an aggravation of the preexisting condition.

For the entire series, unvaccinated cases under similar conditions and delivered by the same personnel served as a control.

The morbidity for the present vaccinated group was 4.24 per cent (that is, for 471 cases) and 4.6 per cent for the combined group including the 502 vaccinated cases previously reported (total—973 cases).

The morbidity for the nonvaccinated group in this series of 471 cases was 17.1 per cent and for the combined group including the cases previously reported it was 19.66 per cent.

### SUMMARY

A method has been presented whereby a vaccine was prepared and used in an attempt to immunize a series of pregnant women: series 1, 51 cases, series 2, 177 cases, series 3, 274 cases, and series 4 (present report), 471 cases, total 973 cases. The following points may be considered salient features of these studies:

- 1 Active immunity was conferred to mice by means of repeated injections of vaccine.

- 2 The safety and absence of reactions to the vaccine were demonstrated.

- 3 Preexisting conditions in these cases, whether acute or chronic, were not aggravated by vaccination.

- 4 In the entire four series which includes the present report, 973 patients were delivered with no fatalities. In a communication with the Philadelphia County Medical Maternal Mortality Committee, it was noted that in the years 1935 to 1944, inclusive, there had occurred

441 maternal deaths due to puerperal sepsis. The puerperal morbidity was 4.6 per cent as compared with a morbidity of 17.1 per cent in nonvaccinated cases.

In conclusion, I wish to state that a larger series of patients are being vaccinated, and that special studies were conducted on vaccinated pregnant women, and on a large group of vaccinated medical students (all males) and it was determined by serological tests that in both groups there was a definite and significant rise in antibody titer. These last two studies, which were conducted in cooperation with Dr George P. Blundell, will be reported in detail in the future.

## BIBLIOGRAPHY

1. Dick, G. F. and Dick, G. H. J.A.M.A., 81 1166, 1923 *ibid.*, 83 84 1924; *ibid.*, 84 802 1925; *ibid.*, 84 1477 1925 *ibid.*, 85 1693 1925
2. DeLee, J. B. Textbook of Obstetrics, ed 6, Philadelphia, W. B. Saunders Co
3. Koehler and Ehrenfest. Therapy of Puerperal Fever. St. Louis, C. V. Mosby Co., 1925
4. Adair Fred L. Am J Obst. & Gynec., 29 384 1935
5. Feiner David Am J Obst. & Gynec., 29 444 1935
6. Bernstein, J. B. and Otten, R. E. Vaccination During Pregnancy as a Prophylaxis Against Puerperal Infections. Pennsylvania M. J., May, 1942 (Jan) 1936.
7. Bernstein, J. B. and Bland, G. W. Vaccination During Pregnancy as a Prophylaxis Against Puerperal Infections. Pennsylvania M. J., August, 1939
8. Bernstein, J. B. and Bland, G. W. Vaccination During Pregnancy as a Prophylaxis Against Puerperal Infections. Pennsylvania M. J., May 1942
9. Communication Philadelphia County Medical Society—Maternal Mortality Committee.
10. Bernstein, J. B. and Blundell, G. P. Serological Determination of Antibody Titre in Vaccinated Pregnant Women (to be published)
11. Bernstein, J. B. and Blundell, G. P. Serological Determination of Antibody Titre in Vaccinated Medical Students (Male) (to be published)

# SOME PSYCHIATRIC PROBLEMS IN OBSTETRICS AND GYNECOLOGY

## Diagnosis and Treatment

JOSEPH C YASKIN, M D \*

THE aim of this presentation is to discuss the psychiatric aspects of some of the problems in obstetrics and gynecology in a manner that will enable the clinician to attain a classified idea for purposes of diagnosis and treatment. To accomplish this, the clinician need acquire a few principles in psychopathology and psychotherapy which are as essential in psychiatry as are anatomy, physiology, chemistry, pathology, pharmacology and surgical technic in organic medicine and surgery

### SOME BASIC PRINCIPLES IN PSYCHOPATHOLOGY

To understand the psychiatric aspects of his individual specialty, the clinician must possess a few principles regarding the structure and function of personality, types of personality, the various reaction types and in the case of the neuroses, some psychological mechanisms. These will be briefly defined and discussed.

**Personality.**—Personality is the sum total of all the reactions in a given individual. It includes the habitual patterns of behavior of the individual in terms of physical and mental activities and attitudes (Healy, Browner and Bower<sup>1</sup>). Personality is *dynamac* from birth to death. Its development begins with the *instincts* inborn, unlearned drives which though repressed, suppressed and modified in many ways, remain the great driving force of the personality. The cementing and supporting energy of the *instinctual* drives is emotion. In the course of development there is a constant struggle between the inborn tendencies on one hand, and the demands of the outside world on the other. This everlasting struggle determines impulse, temperament and character and the modes of thinking, feeling and acting. For the scientifically and organically minded clinicians, one may offer a crude but accurate analogy which may be found in the development and reactions of the various organs in the body.

A fundamental, empirical, but necessary concept of personality necessitates the division of the personality into two parts, *unconscious* and *conscious*. The unconscious monopolizes the greater part of per-

---

From the Department of Neurology and Psychiatry, Graduate Hospital, University of Pennsylvania, Philadelphia.

\* Professor of Neurology, Graduate School of Medicine, University of Pennsylvania.

sonality It has often been compared with the submerged part of an iceberg, the visible part representing the conscious. The unconscious is defined as a deep level of mental activity consisting of elements which never were conscious (collective unconscious of Jung<sup>2</sup>), and of elements previously in consciousness but forgotten, suppressed or repressed. *Suppression* is a purposive exclusion of ideas from the field of conscious attention. *Repression* is an unconscious exclusion of painful and unpleasant material from consciousness and from motor expression. Repression is directly or indirectly accomplished by that part of the personality which is concerned with the adaptation of the individual to the needs of reality The unconscious is brought into consciousness only in dreams, abnormal states and by special psychological technic. The conscious part of the personality is at all times markedly influenced by its larger unconscious part.

It should be stressed that the unconscious is not a static, inert mass. It is a form of energy and, as such, has *dynamic* possibilities This energy, accumulated as it is in the course of adaptation and development from infancy onward, is incorporated into certain units called *complexes* A complex is an unconscious constellation of ideas held together by an affective (emotional) charge and therefore in some way related to instinctive processes. Most of the unconscious consists of material which is evolved in successful integration. Some of the complexes are residues of poorly solved conflicts which are excluded from consciousness due to their lack of harmony with the conscious part of the personality and its tendencies. These complexes, which are poorly integrated in the personality, usually develop early in life, and frequently have their origin in reactions peculiar to earlier life. These reactions consist of phantasies, incidents and situations which have their origin in childhood and which are forgotten but are projected into adult life in a symbolic form (Yaskin<sup>3</sup>)

Poorly integrated parts of the unconscious express themselves in dreams, in sublimations, in character traits and in the presence of *precipitating* causes, in *symptom* formation. These symptoms may be in the physiological or psychological spheres, or both The manifestations are usually in the form of disguises or symbols which have no clear semblance to the original situation any more than universal edema has to the failing kidney

When one considers the personality from this viewpoint, it is easier to understand how a given physiological disturbance is a symbol of a psychological disturbance which can only be understood when the personality is properly evaluated Without such an approach, both diagnosis and treatment are unsatisfactory

**Types of Personality**—It is highly desirable but difficult to classify personalities into types. For the present the author in practice uses the following classification, which is undoubtedly open to many objections but which has been found useful, nevertheless

1 **AVERAGE NORMAL.** This may be defined as the type who makes a satisfactory economic, social, marital and sexual adjustment, who performs efficiently without symptoms or marked emotional swings, who most of the time gets satisfaction from his life experiences, and whose reactions to various stresses and strains are adequate and efficient.

2 **NEUROTIC PERSONALITY** The neurotic personality is characterized by manifestations intermediate between normal character traits and neurotic symptoms (Jones<sup>4</sup>) In the neurotic personality the "neurosis is built into the character" The neurotic symptoms vary considerably with the type of neurosis and will be discussed later Here it may be well to emphasize some features more or less universal in all neurotic personalities The basic psychopathologic process is one of *anxiety* or its many modifications or substitutes *Hostility*, overt or concealed, is often present The neurotic traits always develop *early in life*, are modified by the many life experiences, usually manifest themselves by subtle attitudes and reactions, and become *symptoms* under the impact of appropriate precipitating causes

3 **SYNTONIC TYPE (Cycloid, Extraverted)** This is characterized by swings of mood beyond those observed in the average normal The moods in these individuals determine the behavior in their everyday activities The syntonetic type is a predisposing cause to manic-depressive reactions

4 **SCHIZOID TYPE (Shut-in, Introverted)** A good description of this type is at present not available These individuals are characterized on the one hand by marked sensitiveness and on the other by unapproachable coldness Regardless of the proportion of these qualities, the schizoid *lives within himself* (Noyes<sup>5</sup>) This type of personality is apt to develop dementia praecox

5 **PARANOID TYPE.** This is characterized by the tendency to misinterpretation, abnormal suspicion, and stubbornness, and by consequent mood and behavior disturbances leading to poor adjustment This type is apt to develop dementia praecox and paranoid reactions of other types

6 **RIGID TYPES** This type of an individual is overly serious, overconscientious, overmeticulous, strictly conventional, abnormally honest, preoccupied with problems of security and generally engrossed in immediate problems so that the future horizon is rather circumscribed This type is more common in women and is apt to develop involution melancholia

7 **CONSTITUTIONAL PSYCHOPATHIC TYPE.** This type of individual is neither insane nor intellectually deficient These individuals lack emotional and volitional stability, and "stick-to-itiveness," and do not benefit by experiences, so that they make poor economic, social and marital adjustments They include the pathological liars and swindlers, the nomadic personalities, the antisocial individuals, some paranoid types and some sexual psychopaths

**Reaction Types**—The various mental reactions are intimately related to the various personality types From the standpoint of psychopathology it is well to be familiar with the several reaction types These include

1 The *organic* reaction type, such as occurs in structural diseases of the brain due to vascular and degenerative changes, neoplasms, infections, intoxications and deficiency states, and characterized by psychotic, predominantly intellectual, difficulties

2 The *affective* reaction type, comprising principally the cyclic manic-depressive reactions and involutional melancholia

3 The *schizophrenic* reaction type, with many bizarre modes of thinking, feeling and acting observed in various types of dementia praecox

4 The *psychoneurotic* reaction type, which is the most frequent type and

should be understood by all clinicians. The psychoneuroses and neuroses may be defined as conditions characterized by a variety of subjective complaints without any primary structural or chemical causes to account for their existence and generally traceable to some disturbance in the psychological processes of the individual. In the psychoneuroses the causative factors are traceable to occurrences and phantasies of early life with reactions to these incidents in the form of personality traits. In the neuroses the causative factors are traceable to occurrences or situations in the recent past or immediate present. In this presentation the term "neuroses and psychoneuroses" will be referred to as "neuroses."

The psychopathology of the neuroses is complex and for detail the reader is referred to other publications (Yaskin<sup>6</sup>). Here it may be well to submit the following formulations. For practical purposes the concept neurosis implies the absence of any primary structural or chemical disease, the existence in the majority of cases of a certain constitutional make up (the predisposing cause), the occurrence of precipitating or exciting causes, and the formation of symptoms which may be in the psychic or in the physiologic sphere, or both.

From the standpoint of the neuroses, the most important aspect of the personality is the emotional (affective) reaction. These emotional reactions may have their origin in situations of which the patient is perfectly aware (in the conscious) or in occurrences of phantasies of the past of which he is totally unaware (in the unconscious). The existence of the unconscious has not been proved but, at present, it is a necessary hypothesis in the management of the neuroses. The unconscious activities of the personality are comparable to the activities of most of the thoracic and abdominal viscera of which we are not normally aware but which nevertheless exert a determining influence on our very lives. It is only when the viscera become disturbed that we become aware of them by reasons of symbols which we call symptoms. Symptoms in organic medicine are often clever disguises, as edema in Bright's disease, glycosuria in pancreatic disease, and so on. It has taken thousands of years to correlate the bizarre symbols with their true causes. This tendency for nature to disguise and symbolize is even more marked in psychopathology and makes the subject at times very complex, but, just as in organic medicine, there is always a chain of events to account for the occurrence of the various phenomena. Most of us can as easily understand the occurrence of tachycardia, vomiting, diarrhea or fainting as an immediate result of some great emotional shock as easily as we understand vomiting in obstruction of the gastrointestinal tract or the tachycardia in the failing heart. Some may doubt that insomnia, abnormal fatigability and irritability, phobias and many visceral disturbances are entirely due to emotional disturbances which occurred years before the development of the symptoms, although none of us at present question that tabes and other marked changes in the various organs had their origin in a humble small cutaneous lesion called a chancre. It is a fact, nevertheless, that many neurotic symptoms are prolongations of early emotional

states which remain dormant in the unconscious part of our personalities until some exciting cause activates them

Symptom formation results from the action of some exciting cause which may be an injury, infection, a chemical disturbance or some emotional stress. The symptoms may continue long after the exciting cause ceases to operate, and thus represent released phenomena of the neurotic traits of the previously apparently well integrated personality. These symptoms include either frank anxiety states or symptoms tending to avoid anxiety such as conversion, compulsive-obsessive neurotic reactions. These symptoms vary in severity from a slight headache, increased fatigability and irritability, to devastating visceral disturbances, intractable insomnia with marked agitation, and alarming loss of weight. The clinical manifestations frequently completely overshadow the primary constitutional factors or the immediate precipitating mechanisms.

*Anxiety* is the central symptom of nearly all the neuroses and psychoneuroses and is of fundamental importance in the management of all neuroses. Anxiety may be defined as one of the clinically important major emotions recognized introspectively as an unpleasant feeling, accompanied by fear without any, or without adequate cause, and manifested objectively by abnormal changes in the neuromuscular, autonomic, and secretory functions (emotional expressions). All neurotic symptoms are derived from anxiety arising in the conscious or unconscious parts of the personality. These symptoms include frank anxiety or conversions and substitutions for anxiety reflected in disturbances in the physiological or emotional spheres.

There are many mechanisms by means of which anxiety is converted into symptoms and those interested will search for these in publications on psychopathology.<sup>1</sup> Here it is worth stressing the role that *hostility* plays in a good many neurotic conditions. Anxiety gives rise to hostility, which in turn generates more anxiety and thus a vicious circle is established. Both the anxiety and hostility are experiences of which the patient is not at all or only poorly aware. The existence of both anxiety and hostility help to explain the reasons why "the neurotic person may at the same time be driven imperatively toward dominating everyone, toward complying with others and imposing his will on them, toward detachment from people and craving for their affection. It is these utterly unsolvable conflicts which are most often the dynamic center of the neuroses. The two attempts which most frequently clash are the striving for affection and the striving for power" (Horney<sup>7</sup>).

It is well to remember that a given group of symptoms is only a conspicuous part of the total neurosis and that the several types of neuroses differ considerably in their etiology, psychopathology, prognosis and treatment.<sup>1 6</sup>

## PSYCHOTHERAPY

Psychotherapy is a procedure which aims to correct the underlying psychopathic difficulties as well as the various symptoms of which the patient complains. It is a psychologic device used to change the attitude of the patient toward himself, toward his physical and mental processes, and toward his environment. It is an attempt to reevaluate his various life problems in relation to his various symptoms in the light of intellectual and, especially, emotional experiences.

For purposes of systematic description, psychotherapy is divided into the following artificial steps:

*Rapport*—This is a relationship between physician and patient whereby the latter gains confidence in and respect for the therapist, and at least a desire to cooperate despite preconceived notions of the origin of his symptoms. Rapport is indispensable for successful treatment and is probably the most important step in the treatment. To attain the attitude of a satisfactory rapport the patient must feel that the physician not only sympathizes with him but also that he has a clear formulation of his case and has the ability to help him. To justify to the patient's expectations the physician must not be too hasty in arriving at conclusions but once the formulation is made he must remain firm in his statements, betray no doubts or indecisions, and above all be frank and truthful.

*Ventilation or Aeration*—This consists of bringing into conscious attention in specific detail unwholesome attitudes and reactions which are usually associated with irritating memories. Some material is usually elicited in a detailed initial history. More information will be given by the patient when he is permitted to talk freely in direct interviews. Often, however, it is necessary to use the free association method.

*Desensitization*—This consists in removing the unpleasant emotional tone attached to the memories by intellectual discussion. The patient is encouraged to face openly the unpleasant experiences and memories of the past. To accomplish this the material must be brought into consciousness repeatedly. This is done either by direct interviews or by the free association method. In the course of time there is usually a better objective understanding by the patient, and, what is more important, the emotion loses its unpleasant "sting."

The physician should guide the patient in this phase of the treatment. An element of suggestion is neither unavoidable nor undesirable, provided the therapist does not abuse it. It is necessary that the desensitization should be gradual to avoid severe "shock" reaction, avoiding undue wounding of sensitivity and pride, and slowly building up tolerance to unpleasant emotional realizations.

It is best to leave most patients with some formulation at the end of each treatment period.



*Retraining, Reeducation and Stabilization*—This consists in guiding the patient to react more or less automatically in a symptomless, efficient and wholesome manner to various stresses in life. To be more or less automatic the responses have to be free from unpleasant emotional tone. This is accomplished by desensitization, and must be learned, at least in the adult, by persistent conscious effort. As a necessary part of lasting successful retraining and reeducation the patient should be guided to formulate an economic, social and recreational plan which will vary markedly with the individual patient.

*Other Procedures*—Psychotherapy of the family is often an important part in the management of many cases. Included in the several procedures are elements of encouragement, suggestion, rationalization and persuasion irrespective of the type of psychotherapy used. Often the mental illness is complicated by various stresses such as marital, social or economic, which cannot be eliminated and under such circumstances the patient is guided to face the hard facts in the situation and work out some compromise.

In addition to the purely psychological methods the clinician often employs methods which are partly psychological and partly physiological such as a regimen at home or at work, hospitalization, and occupational and physical therapy. Also purely physiological approaches are useful and at times necessary. These include sedatives, somnifacients, narcosis, tonic and endocrine agents, and attention to nutritional and hygienic needs.

The psychotherapy of the different types of neuroses cannot be discussed here and the reader is referred to other publications on this subject<sup>3, 6</sup>

#### PSYCHIATRIC ASPECTS IN SOME SPECIFIC PROBLEMS IN OBSTETRICS

The obstetrician and gynecologist is not expected to have a profound knowledge of psychiatry but should possess a few principles which may be useful in his practice. A knowledge and record of personality make-up, the manner in which the patient thinks, feels and acts, a few notes on the *mood* of the patient at a given examination, the presence of fears, obsessions, compulsions, unusual preoccupations or a tendency to misinterpret, may be helpful in the subsequent management of the case.

There are, in addition, a number of specific problems in pregnancy and in the postpartum period and in gynecologic practice which have definite psychiatric implications, and these will now be discussed in relation to psychopathology and psychotherapy.

*Psychiatric Aspects of Pregnancy*—Pregnancy and the puerperium consume a year of the individual's life, and this in itself is of psychiatric significance. Considering the complexities of our culture, pregnancy, labor and the postpartum period have major psychiatric implications and, as Piker<sup>8</sup> points out, the obstetrician can no longer confine his

attention to the "pelvic outlet" but must evaluate the total personality of the patient, as experienced obstetricians always have.

*The Normal Woman and Pregnancy*—Many normal women have apprehension regarding the danger of pregnancy and labor, and concerning the child-to-be. These fears are usually based on misinformation and superstitions acquired earlier in life. Under ordinary circumstances a brief superficial discussion will allay the patient's tension. If the obstetrician becomes aware of considerable tension on the part of the patient she should be permitted to unload her various ideas and be guided by explanation and encouragement to dissipate the tension if not the ideational content. The mere fact that the patient feels that the physician is attentive, sympathetic and reassuring will go a long way to reduce her emotional tension.

The normal woman may not want a child or additional children for many reasons and when confronted with pregnancy, may become tense and resentful. The situation may be further complicated by unsuccessful attempts at abortion and fears about the ill effects on the offspring. Most of these cases react favorably to common sense guidance by the psychiatrically minded obstetrician.

*The Psychoneurotic Woman and Pregnancy*—Women are often advised to become pregnant in order to improve their psychoneurotic state. This as a rule is poor advice. It is a clinical fact that during pregnancy especially after the first weeks, the psychoneurotic feels at her best. As a rule, however, the added responsibility of the offspring, in the inadequately treated psychoneurotic, causes a marked exacerbation of symptoms. The much better plan is to treat the psychoneurotic first and long enough for her to procure a good insight into her neurotic problems so that she feels the urge to give enough of herself to have a child and assume the responsibility that goes with motherhood. This is especially true of women whose marriage was delayed for years by phobias, compulsions and obsessions. In these women the desire to have an offspring is an indication of satisfactory progress in psychotherapy and indicative of satisfactory adjustment in many phases of their lives.

In the majority of psychiatrically untreated cases, the psychoneurotic condition becomes worse with pregnancy. To begin with, in many cases the pregnancy is unwanted, consciously or otherwise. There are many conscious reasons for this attitude: illegitimate pregnancy, fear of disfigurement, fear of forthcoming responsibility, fear of being made to give care to the home and children, economic factors and many more understandable situations. In many cases the child is not wanted for unconscious reasons, although overtly the anxiety to avoid pregnancy is subtly masked by pretense to have an offspring. The fear or resentment of pregnancy in these cases is traceable on the one hand to the constitutional factors of the neurosis, especially phobic and compulsive-obsessive tendencies, and, on the other hand to situa-

for transient delirium. Lastly, idiosyncrasies to drugs undoubtedly account for some transient delirious states.

In general, it may be stated that the organic type of reaction, if the cause can be removed, is of relatively brief duration and the recovery is complete. If the cause is removed and the mental disturbance persists, it is reasonable to assume that there is a constitutional factor responsible for the psychotic reaction.

The *manic-depressive* reactions are most commonly encountered. The onset of the psychosis is usually between the first and fourteenth day postpartum, although in some cases the symptoms may be evident before delivery or may not appear for weeks after delivery. The onset may be sudden but is usually gradual. The patient exhibits some personality changes with increase in tension, undue anxiety, restlessness, irritability, disturbances of sleep and more particularly changes in mood. The condition then develops into either a depression, often masked by somatic complaints (Denison and Yaskin<sup>12</sup>), or into a manic phase. In the depressed patients suicidal ideas and actual attempts at suicide are not uncommon. In the manic phase, overtalkativeness and often harmfully poor judgment are exhibited.

In the *schizophrenic reaction* the time and mode of onset may be the same as in the manic-depressive. Here the personality changes may be even more marked with considerable general discontent, marked tension and apprehension and other mood changes. But in addition, there often are present suspiciousness, tendency to misinterpretation, phobias, hallucinations and infanticidal ideas.

The *predisposing causes* of the various types of psychoses are to be found first and foremost in the personality make-up. The *exciting causes* in the relatively infrequent organic type of reaction are found in the various conditions above enumerated. Among the exciting factors in the manic-depressive and schizophrenic reactions, the following may be mentioned: long-continued economic stress, incompatibility between marital partners, undesired pregnancy, a feeling of inadequacy about the responsibility of motherhood, and a previously sheltered life (Ordway and McIntire<sup>13</sup>).

The *prognosis* of the postpartum psychosis varies with the type. Recovery is complete in the organic cases which survive the underlying physical factors. The manic-depressive patients recover if they do not commit suicide or succumb to intercurrent disease, but recurrences are quite common with or without subsequent pregnancies, perhaps more so with subsequent pregnancies. The prognosis in the schizophrenic group is unfavorable. Social recovery occurs in only 15 to 30 per cent of cases and the likelihood of exacerbation of the process is great with subsequent pregnancies.

The *treatment* of the postpartum psychosis does not vary from other types of psychotic reactions. In the organic type the early recognition of the physical factors is of great importance since the recovery in

these cases depends largely on the removal of these factors. Careful physical examination and laboratory studies should be performed on every patient who develops psychotic reactions after childbirth. In the presence of a delirium, repeated studies should be performed. Temperature readings and complete blood counts are often helpful in doubtful cases.

Early diagnosis of schizophrenia and especially manic-depressive reactions is highly desirable. The obstetrician who knows the personality make up of his patient for months prior to delivery is in excellent position to recognize the early symptoms and be instrumental in starting early treatment. This is particularly important in cases exhibiting suicidal and infanticidal tendencies.

The depressed patient is to be particularly guarded because of the danger of suicide. Moreover, the more severe types of depression are readily amenable to electrocerebral shock therapy which may be commenced about four to six weeks after delivery. With this form of treatment about 60 per cent of the cases make complete recovery within four to six weeks. Those which do not respond last from six to nine months. The manic patient recovers spontaneously in six to nine months and is less amenable to shock therapy, which should be reserved for very severe manic patients.

The treatment of the schizophrenic patient is less satisfactory. In some cases insulin shock therapy is used.

Psychotherapy has its place in the treatment of the psychoses but compared with the shock forms of treatment or with its efficacy in the psychoneuroses it is of less value.

*The Problem of Termination of Pregnancy*—The question of termination of pregnancy in one who has had a psychosis in the postpartum period and the whole matter of contraception and sterilization for therapeutic purposes is so entangled in popular and religious attitudes, as well as in its medicolegal complications and the problems concerning hereditary transmission, that it cannot be settled at present. Generally speaking, however, it would not seem advisable for a woman who has had a psychosis following childbirth to have more children since another childbirth might well precipitate another psychotic episode or activate a quiescent psychosis (Cohen<sup>14</sup>). Yet, in my experience, women who have had manic-depressive episodes following childbirth have had one, two and three children thereafter without psychotic reactions and at least one woman who had a schizophrenic reaction after the birth of the second child had two subsequent pregnancies without mental disturbance.

#### SOME PSYCHIATRIC ASPECTS IN GYNECOLOGY

*Menstrual Disturbances*—There are many psychological aspects to menstruation. Chadwick,<sup>15</sup> in her monograph on the Psychological Effects of Menstruation, indicates convincingly that all races have shown

guilt over menstruation and according to their folklore they have needed some impersonal or plausible way to explain its occurrence. The ancient idea that the monthly flow of blood was accompanied by cruel and hostile wishes within the woman led to many taboos erected against her, as is well portrayed in the Old Testament. The psychiatrist often sees it in our own culture, through phantasies, anxieties, superstitions and hostilities in the individual patient. These psychological factors may be overt or may be highly symbolized.

*Dysmenorrhea*—The experienced gynecologist has learned that many cases of dysmenorrhea are functional, that is, not due to any discernible organic or biochemical causes. He learned by experience to avoid useless operative procedures. Functional dysmenorrhea may be one of the many manifestations of the neurotic make-up or, like migraine, a monosymptomatic manifestation of a deep-seated neurosis. Wengraf<sup>16</sup> considers functional dysmenorrhea as an organ neurosis exhibiting the following characteristics: (1) absence of demonstrable pathology, (2) inconstancy, the pain varying from month to month, mostly as a reaction to pleasant or distressing events, (3) reversibility, (4) connection with neurotic symptoms, (5) amenability to diverse therapy, and (6) amenability to suggestion and hypnosis. Menstruation becomes the realization of old guilt feelings directed particularly toward the mother. Dysmenorrhea manifests suppression and conversion symptoms. It may be exhibited in three spheres: local, including backache and urinary or rectal disturbance, general complaints involving the cerebrum and/or abdominal and secondary sexual organs, and psychosexual. Frigidity is a frequent accompaniment. Cessation of menstrual cramps, if the psychogenic factors remain, may mean only that the neurosis is finding expression in another form. Kroger and Freed<sup>17</sup> have cured dysmenorrhea by hypnosis. While these authors are perhaps unique in pioneering in their views, there can be little doubt that some cases of functional dysmenorrhea may be favorably influenced by judicious psychotherapy. Here, as in other psychosomatic situations, simpler methods should be resorted to prior to plunging the patient into time-consuming expensive, psychological procedures.

*Amenorrhea*—Amenorrhea as a psychiatric problem has received little attention in the literature. Although not relevant to the subject I should like to stress that amenorrhea may antedate other evidences of a pituitary tumor by months or years. Amenorrhea is not uncommonly due to major emotional disturbances and is particularly common in the major psychoses such as depressions and schizophrenic reactions. It may be the earliest clinical manifestation of a beginning psychosis.

I should like to stress that the amenorrhea of the psychoses has no etiological significance and that the patient need not be subjected to therapy to bring on the menstrual flow. With recovery from the psychosis, menstruation becomes reestablished.

**Sterility**—The psychological study of sterility in women has thus far received little attention. It has long been observed that conception may occur in a previously sterile woman after she has adopted a child. Bear<sup>18</sup> discusses this problem and expresses the opinion that following the adoption of a child some change in the mode of life situation, but without discernible changes in their structure or physiology, follows, and conception takes place. He urges psychiatric studies in cases of sterility in which no satisfactory gynecological causes for the sterility can be found.

**Frigidity**.—Varying degrees of frigidity are quite common and are important from a psychiatric standpoint. While frigidity in itself is not a serious "symptom" it often becomes the cause of marital disharmony. Frigidity in the psychoneurotic is of great prognostic importance, and the woman who remains frigid after treatment usually makes unsatisfactory improvement.

Weiss and English<sup>19</sup> classify frigidity into the following grades: occasional failure to achieve orgasm, only occasional orgasm, mild pleasure in intercourse but no orgasm, vaginal anesthesia with no special aversion to coitus, vaginal anesthesia with aversion to coitus, and dyspareunia and vaginismus.

They suggest the following causes for frigidity: fear of disapproval or punishment, hostility toward the partner, conflicting loves (usually unconscious), latent homosexuality, and too much self-love.

In the treatment of the various grades of frigidity, it should not be forgotten that many cases are due to organic conditions, including organic disease of the nervous system and the endocrine apparatus. However, every psychiatrist knows the role of frigidity in the structure of the psychoneuroses and realizes that in the course of psychotherapy many causative factors come to consciousness and that with the improvement of the psychoneurosis the frigidity becomes less marked or disappears altogether.

I should like to stress that in depressions, especially in the manic-depressive depressions, frigidity is an early and constant symptom. With the disappearance of the depression, normal sexual attitudes and reactions become reestablished.

*Sexual perversions* have many psychiatric aspects and at the present time are of little gynecologic interest. Nymphomaniacs, homosexuals, exhibitionists and the like remain, for the present, largely psychiatric and social problems.

**Psychiatric Aspects of Gynecologic Surgery**—The psychiatric aspects of gynecologic surgery do not differ from the other forms of surgery, especially abdominal surgery, and will be dealt with briefly.

Both surgeon and psychiatrist have long since learned that organic pelvic disease is not a cause for either neurosis or psychosis. The experienced surgeon is keenly aware of the fact that avoidable or elective surgery does not improve the psychoneurotic. He has learned to

caution the neurotic in advising a necessary operation, such as removal of an ovarian cyst or repair of the pelvic floor, that it will have no, or no material, influence on the course of her neurosis. Indeed he learns by experience to have psychiatric guidance when confronted with operations of necessity in severe psychoneurotic states. A promise that a pelvic or abdominal operation will cure a neurosis is due either to dishonesty, lack of knowledge and experience, or both, and is not conducive to benefit to the patient, and, in the long run, to the surgeon.

Surgical procedures in themselves do not produce neuroses or psychoses. Some psychoneurotics are temporarily benefited by the rest, attention and regimen incident to surgical procedures. Many of these patients have an exacerbation of their neurotic symptoms following the surgical convalescence, when confronted with old responsibilities and a return to their faulty attitudes and reactions.

The psychoses that follow surgical procedures are basically the same as those following childbirth, with one exception, that gynecologic procedures in later life are at times followed by presenile, senile and arteriosclerotic dementias and by involution melancholia. In addition to the above-mentioned organic types there are the organic reactions incident to sepsis, hemorrhage, intoxications and exhaustive factors. By far more common, however, are the manic-depressive and schizophrenic reactions, in which cases the operative procedure is merely a precipitating cause in a constitutionally predisposed individual.

**Involution Melancholia**—This is a psychosis occurring most commonly between the ages of 45 and 55, about three times more common in women than men, often beginning with somatic complaints, referable most commonly to the abdominal organs, associated with or followed by depression, agitation, delusions of self-accusation, but occasionally paranoid trends, suicidal tendencies and other severe psychotic reactions.

It occurs most commonly in the rigid type of individual, described earlier in this paper. There is no evidence, at present, of any definite structural or biochemical cause for this disease. Despite the voluminous literature to the contrary, I am convinced that involution melancholia has no etiologic relation to the endocrine changes of the menopause, although I do not deny the probability that there may be biochemical factors for this disease and most of the other psychoses.

Prior to the advent of shock therapy, the prognosis of involution melancholia was unfavorable, not more than 50 per cent recovering in from two to four years.

The treatment of involution melancholia, in the absence of contraindications, is electrocerebral shock therapy. From 80 to 90 per cent of these cases recover within a few weeks. The gynecologist can be of great service in suspecting the disease early in its course and thus help to avoid suffering, invalidism, and often suicide. The endocrine

substances may alleviate the flashes and other vasomotor phenomena but do not cure involution melancholia.

### SUMMARY AND CONCLUSIONS

Modern clinical medicine and surgery must take into account the psychological aspects in many problems. To do so the clinician should learn to think systematically in terms of personality make-up, personality types and reaction types. He should possess a few definite principles in psychotherapy and allied suitable methods of treating psychiatric problems. With this in mind, useful psychopathology and psychotherapy were briefly discussed.

The obstetric and gynecologic problems have many psychiatric aspects which hitherto have received too little attention.

The psychiatric problems of pregnancy were discussed from the standpoint of the psychoneurotic and with special reference to the vomiting of pregnancy. The psychotherapy of the psychoneurotic prior to conception, during pregnancy and postpartum, were discussed. The concept of a special puerperal psychosis is no longer tenable. The psychotic reactions following pregnancy are usually manic-depressive or schizophrenic. The organic type of reaction is uncommon but when present should receive careful attention in order to remove the underlying physical causes.

Many gynecologic problems have definite psychiatric aspects. Those briefly discussed include dysmenorrhea, amenorrhea, sterility, frigidity and gynecologic surgery.

Involution melancholia is of particularly great interest to the gynecologist and early diagnosis and treatment were stressed.

### BIBLIOGRAPHY

1. Healy, W., Browner, A. F. and Bowers, A. M. *The Structure and Meaning of Psychoanalysis*. New York, Alfred A. Knopf Inc., 1930.
2. Jung, C. G., *Psychology of the Unconscious*. New York, Moffat, Yard & Co., 1916.
3. Yaskin, J. C., *Psychobiology of Anxiety*. *Psychoanalyt. Rev.*, 23 (July and October) 1936, 24 (January, April and July) 1937.
4. Jones, E., *Anxiety Character*. *Med. Rev. of Rev.*, 36:177, 1930.
5. Noyes, A. P., *Text Book of Psychiatry*. New York, Macmillan Co., 1928.
6. Yaskin, J. C., *The Psychoneuroses and Neuroses, A Review of 100 Cases with Special Reference to Treatment and End Results*. *Am. J. Psychiat.*, 93:107, 1936. *The Treatment of Functional Gastro-intestinal Disturbances of Neuro-psychiatric Origin*. *Ann. Int. Med.*, 18:949-967, 1943, also Ref. 3.
7. Horney, K., *The Neurotic Personality of Our Time*. New York, W. W. Norton & Co., 1937, p. 100.
8. Piker, P., *Psychoses Complicating Childbearing*. *Am. J. Obst. & Gynec.*, 35:901, 1938.
9. Skottowe, L., *Mental Disorders in Pregnancy and the Puerperium*. *Practitioner*, 148:157, 1942.
10. Kraines, S. H., *Treatment of Psychiatric States Following Pregnancy*. *Illinois M. J.*, 80:200-204 (Sept.) 1942.



One 3-ounce bottle of fluidextract of ergot  
 Four abdominal binders  
 Four breast binders  
 Sterile boric acid solution, 1 pint

The next important step is the *selection of the room*. A room which is well lighted, airy, and convenient to lavatory facilities should be selected for the delivery of the patient.

The room should be as spacious as possible and all unnecessary furniture should be removed. All that is necessary is a bed with a firm spring, a bureau, a few straight chairs, and two tables for the reception of those articles which are needed in the conduct of labor and the puerperium.

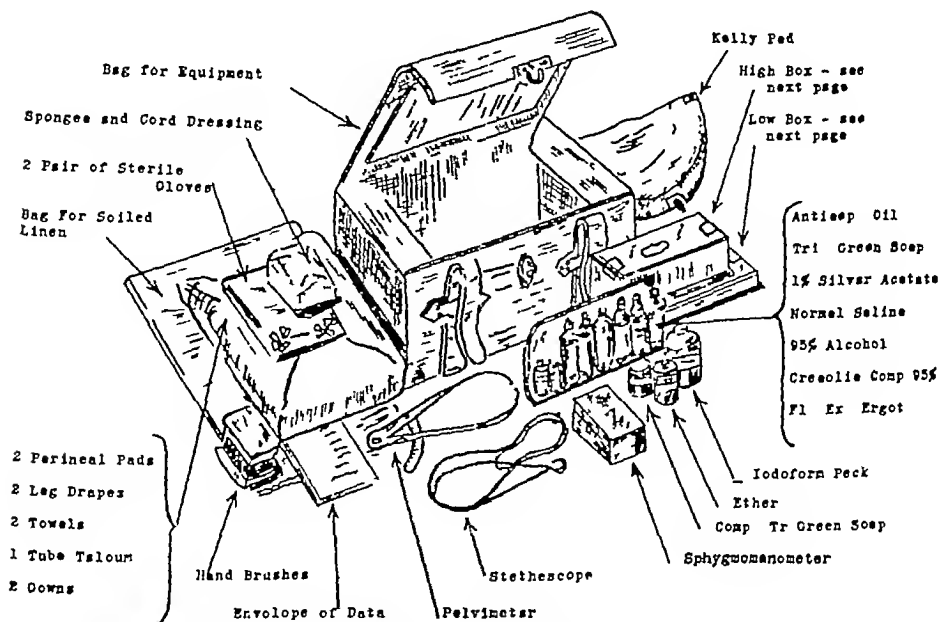


Fig 187—Contents of obstetrical bag (From "Mechanics of Obstetrics" by Vaux and Castallo, F A Davis Co)

As the time of delivery approaches all the furniture should be carefully protected by ample layers of newspapers. The floor around the bed should also be covered with layers of newspaper, and a bucket or basin placed on the floor, at the side of the bed, for the disposal of waste material.

The next important step is the *preparation of the bed*. A narrow bed with firm springs and firm mattress is best adapted to the conduct of labor. If this is not available and the spring sags, an ironing board or extra table leaves should be placed either under the springs or between the springs and the mattress. This is to prevent the accumulation of blood and amniotic fluid in a pool in the center of the bed during the delivery.

A rubber sheet should be placed directly over the mattress, or if one is not available, thick pads of newspapers should be employed to protect the mattress. A linen sheet is placed over the papers or rubber sheeting. During the actual delivery, a Kelly pad is so placed under the patient's buttock as to drain over the side of the bed into a bucket on the floor.

Preparation must be made before labor for the proper care of the baby. A large basket, bassinet or bureau drawer made comfortable with blankets, should be put in one corner of the room. At the onset of labor, a warm bottle should be placed in the blankets to warm them for the newborn child.

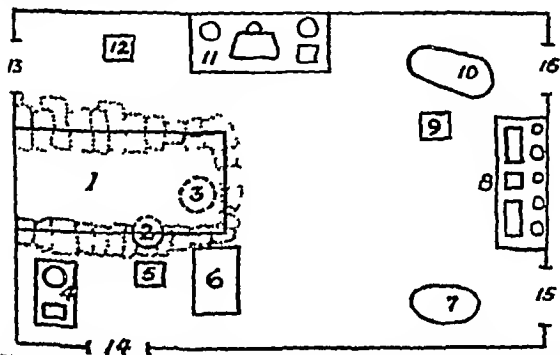


Fig 188—Showing arrangement for delivery in small room. 1 Bed surrounded by newspaper to protect floor. 2 Bucket for disposal of waste, secundines, etc. 3 Basin of lysol. 4 Table of solutions, instruments, etc. 5 Chair. 6. Table for sterile linen, gauze. 7 Basket or bassinet prepared with warm blankets for reception of baby. 8 Bureau for disposal of medication, hypodermics and other accessories. 9 Chair. 10 Tub. 11 Table for bag other instruments. 12 Chair. 13 Entrance. 14 Doorway to adjacent room. 15 and 16. Windows. (From "Mechanics of Obstetrics" by Vaux and Castallo, F. A. Davis Co.)

During the first stage of labor when the patient is first seen a careful and complete examination should be made. This should cover the patient's general condition, i.e., (1) general appearance, (2) temperature, (3) pulse, (4) respiration, (5) blood pressure, (6) palpitation and auscultation of the heart. Then a determination is made, by a careful abdominal and rectal examination, of attitude, presentation and status of the fetus and the degree of advancement of labor.

There is probably no point which means more to the patient than this careful initial examination on the part of the obstetrician and his assurance that all is well. By this single act, her confidence is gained. No sedative or analgesics can take the place of this.

As soon as labor is started an ample quantity of water should be put to boil in three large containers. One is allowed to cool after boiling for thirty minutes, the second should be kept warm after having boiled for a similar period, and in the third, the enamel basins and pitcher should be sterilized. Hot and cold sterile water are thus made readily available for use during labor.

The instruments should be sterilized by boiling in the special copper container carried in the obstetrical bag. After the water is drained, this container should be kept covered until the time of delivery.

*Preparation of the patient* is done at this time. Her hips are elevated on a bed pan. A sterile cotton sponge moistened with lysol solution is inserted in the introitus to prevent the entrance of infective material. The adjacent parts are then washed with a solution of green soap and lysol.

The pubic and vulvar hair is then shaved from above downward. When all the hair has been removed, the pubis, vulva, perineum, and inner margins of the thighs are thoroughly scrubbed with a solution of green soap and lysol, using sterile gauze or cotton.

The bladder should be catheterized only when its distention is such that it interferes with the mechanism of labor. If the rectum is distended with fecal material, a low enema should be administered before the perineum and vulva are prepared.

*First Stage of Labor*—During the first stage of labor in normal presentation the patient may walk about freely or sit in a chair. She is encouraged to take nourishment which is readily assimilated, such as various forms of carbohydrates, fluids in the form of water, weak tea with sugar, fruit juice or ginger ale. The patient should be cautioned against endeavoring to "bear down" with the pains of the first stage.

*Second Stage*—During the second stage of labor, the obstetrician should be in constant attendance upon the patient, or within ready call. Abdominal examination should be repeated at frequent intervals to determine the strength and frequency of labor pain, degree of descent of present part and condition of fetal heart sounds. Rectal examination should be frequently done to confirm the station of the presenting part and determine the degree of dilatation of the cervix. Vaginal examination is to be employed only under special indications.

#### FINAL PREPARATION FOR DELIVERY

In the case of a multiparous patient, preparations for delivery are made when the pains become of a bearing-down character and the cervix is from 4 fingerbreadths to completely dilated.

In the case of a primigravida, preparations for delivery are made when bulging of the perineum is noted.

The physician's outer clothing and shoes should be replaced by an operating shirt, trousers and shoes. His hands must be scrubbed for

ten minutes, preferably under running water. They should then be immersed in 70 per cent alcohol solution. A sterile gown and sterile gloves are put on.

The patient is placed in bed in the dorsal posture with a sterile square of linen on her abdomen and one beneath her hips. The inner side of the thighs, vulva and perineum are cleansed with green soap and lysol solution. A sterile sheet is placed on the lower half of the bed and a similar sheet across the abdomen. The patient's lower extremities are ensheathed in leg covers.

The instruments and solutions are arranged on tables near the foot of the bed. The preparations are now complete for the actual birth of the child.

#### DELIVERY OF THE CHILD

In spontaneous labor it is best to let the patient's feet rest on the surface of the bed until delivery. Then she is placed across the bed with legs over the back of chairs so that she may have some anchorage during her pains and until delivery is consummated.

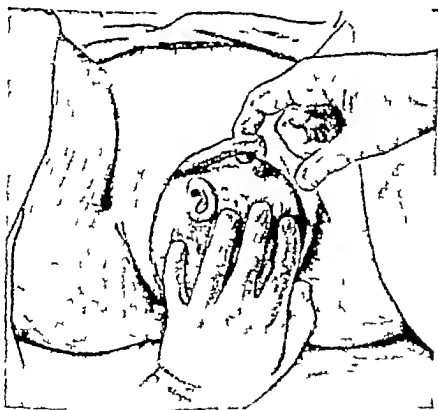


Fig. 189—Disengaging the cord from about the baby's neck. ("Mechanics of Obstetrics" by Vaux and Castallo F. A. Davis Co.)

As the presenting part distends the vulva, care should be taken to avoid extensive lacerations, by placing one hand against the fetal head to restrain it from too rapid expulsion across the perineum. The other hand is employed to lift the head over the perineum by the "maneuver."

When the head of the baby is born, the mucus and amnion are wiped from the nose and mouth and the neck is freed.

As soon as labor is started an ample quantity of water should be put to boil in three large containers. One is allowed to cool after boiling for thirty minutes, the second should be kept warm after having boiled for a similar period, and in the third, the enamel basins and pitcher should be sterilized. Hot and cold sterile water are thus made readily available for use during labor.

The instruments should be sterilized by boiling in the special copper container carried in the obstetrical bag. After the water is drained, this container should be kept covered until the time of delivery.

*Preparation of the patient* is done at this time. Her hips are elevated on a bed pan. A sterile cotton sponge moistened with lysol solution is inserted in the introitus to prevent the entrance of infective material. The adjacent parts are then washed with a solution of green soap and lysol.

The pubic and vulvar hair is then shaved from above downward. When all the hair has been removed, the pubis, vulva, perineum, and inner margins of the thighs are thoroughly scrubbed with a solution of green soap and lysol, using sterile gauze or cotton.

The bladder should be catheterized only when its distention is such that it interferes with the mechanism of labor. If the rectum is distended with fecal material, a low enema should be administered before the perineum and vulva are prepared.

*First Stage of Labor*—During the first stage of labor in normal presentation the patient may walk about freely or sit in a chair. She is encouraged to take nourishment which is readily assimilated, such as various forms of carbohydrates, fluids in the form of water, weak tea with sugar, fruit juice or ginger ale. The patient should be cautioned against endeavoring to "bear down" with the pains of the first stage.

*Second Stage*—During the second stage of labor, the obstetrician should be in constant attendance upon the patient, or within ready call. Abdominal examination should be repeated at frequent intervals to determine the strength and frequency of labor pain, degree of descent of present part and condition of fetal heart sounds. Rectal examination should be frequently done to confirm the station of the presenting part and determine the degree of dilatation of the cervix. Vaginal examination is to be employed only under special indications.

#### FINAL PREPARATION FOR DELIVERY

In the case of a multiparous patient, preparations for delivery are made when the pains become of a bearing-down character and the cervix is from 4 fingerbreadths to completely dilated.

In the case of a primigravida, preparations for delivery are made when bulging of the perineum is noted.

The physician's outer clothing and shoes should be replaced by an operating shirt, trousers and shoes. His hands must be scrubbed for

ten minutes, preferably under running water. They should then be immersed in 70 per cent alcohol solution. A sterile gown and sterile gloves are put on.

The patient is placed in bed in the dorsal posture with a sterile square of linen on her abdomen and one beneath her hips. The inner side of the thighs, vulva and perineum are cleansed with green soap and lysol solution. A sterile sheet is placed on the lower half of the bed and a similar sheet across the abdomen. The patient's lower extremities are ensheathed in leg covers.

The instruments and solutions are arranged on tables near the foot of the bed. The preparations are now complete for the actual birth of the child.

#### DELIVERY OF THE CHILD

In spontaneous labor it is best to let the patient's feet rest on the surface of the bed until delivery. Then she is placed across the bed with legs over the back of chairs so that she may have some anchorage during her pains and until delivery is consummated.

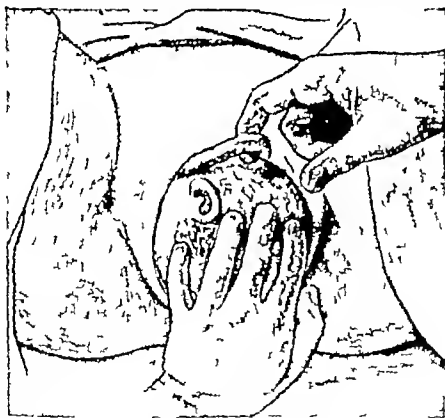


Fig. 189—Disengaging the cord from about the baby's neck. ("Mechanics of Obstetrics" by Vaux and Castallo F. A. Davis Co.)

As the presenting part distends the vulva, care should be taken to avoid extensive lacerations, by placing one hand against the fetal head to restrain it from too rapid expulsion across the perineum. The other hand is employed to lift the head over the perineum by the Ritgen maneuver.

When the head of the baby is born, the mucus and amniotic fluid are wiped from the nose and mouth and the neck is freed from the

restraints of the encircling coils of the umbilical cord. Generally the cord can be slipped over the baby's head (Fig 189). If this fails, however, the cord may be slipped back over the shoulders during birth. If the cord is too tight for either maneuver, it may be cut between hemostatic clamps.

Haste should not be employed in the delivery of the shoulders, the latter are generally expelled spontaneously. If expulsion of the shoulders is unduly delayed, the fingers may be hooked over the fetal head, and steady, firm traction exerted posteriorly in order to bring the



Fig 190—Method of drawing down the anterior shoulder beneath the symphysis pubis ("Mechanics of Obstetrics" by Vaux and Castallo, F A Davis Co.)

anterior fetal shoulder under the symphysis pubis (Fig 190). The fetal head is then drawn anteriorly to deliver the posterior shoulder across the pelvic floor and perineum (Fig 191).

After the complete expulsion of the child, the attendant waits until pulsation of the cord has stopped. During this interval the baby should be held by the ankles with head dependent, in order to drain fluid from the respiratory tract. The free hand of the operator may be employed to gently "milk" fluid from the trachea.

The hand of the operator or of an assistant should be placed fre-

quently upon the maternal abdomen to make sure that the uterus becomes properly retracted around the placenta, and to note changes in contour which subsequently take place.

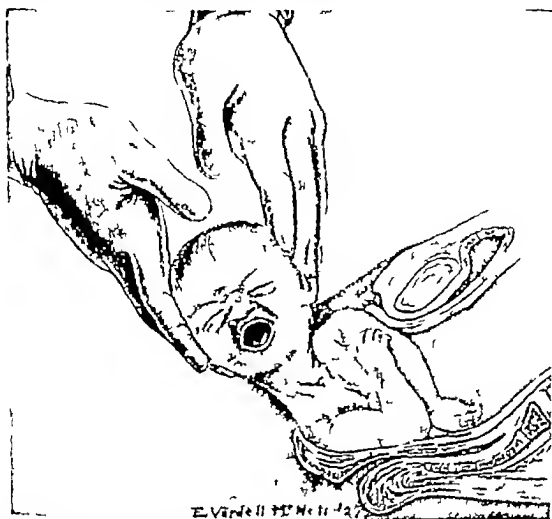


Fig 191—Method of delivering the posterior shoulder across the perineum after the anterior shoulder has been impinged under the pubis. ("Mechanics of Obstetrics" by Vaux and Castallo F. A. Davis Co)

#### CARE OF THE BABY

When the pulsation of the cord has ceased, two hemostatic clamps are applied, one 2 inches from the navel of the baby and the other a half inch distal to it. With the hand interposed as a protection between the fetal body and the scissors, the cord is cut between clamps. Two ligatures of cotton tape are applied and tied firmly, the first 1 inch from the baby's navel and the second in the groove formed by the proximal hemostatic clamp. A sterile dressing moistened with 70 per cent alcohol is applied to the stump of the cord. The dressing is held in place by a band of sterile gauze.

The obstetrician must assure himself that the air passages of the child are clear. This is accomplished first, by holding the child dependent by the legs and gently milking the trachea; second, by employing a suction apparatus or tube to draw fluid or mucus from the pharyngeal region of the baby; third, by inserting, in extreme cases,



a small silk intratracheal catheter and withdrawing plugs of mucus from the trachea (Fig 192)

**Treatment of the Eyes**—The baby's eyes should be treated as soon after delivery as possible. If the obstetrician has assistance, he may do this while he is waiting for the delivery of the placenta. Each eye

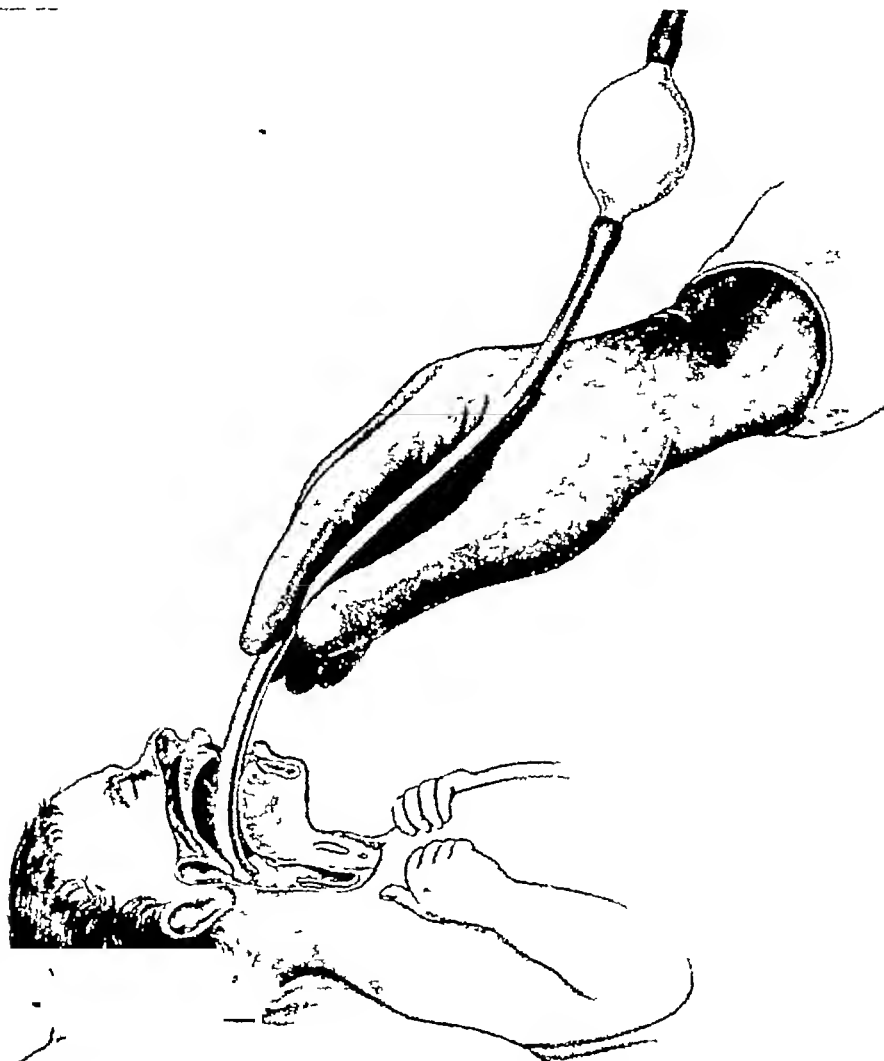


Fig 192—Aspiration of pharyngeal mucus in the newborn ("Mechanics of Obstetrics" by Vaux and Castallo, F A Davis Co)

should receive one or two drops of 1 per cent fresh solution of silver nitrate (1 per cent silver acetate also is used) into the conjunctival sac (Figs 193 and 194). Care must be taken that the eyelids of the baby be sufficiently separated for the silver nitrate to actually enter the sac. An eyelid retractor, such as the Castallo, may be used. After two or

three minutes, the excess of silver nitrate is flushed out with physiologic salt solution. This final step lessens the incidence of chemical conjunctivitis.

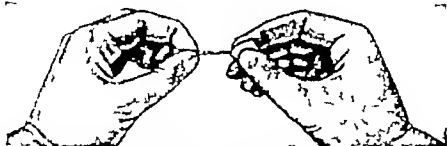


Fig 193—Perforating a wax ampule in preparation for the Credé prophylactic treatment of the newborn's eyes ("Mechanics of Obstetrics" by Vaux and Castallo, F. A. Davis Co.)

The physician, having assured himself that air passages of the child are clear and the eyes treated, wraps the child in a warm sterile towel, or a square of sterile linen, and the child is placed in its warm crib.



Fig 194—Showing method of instilling silver nitrate solution in infant's eyes from paraffin capsule. ("Mechanics of Obstetrics" by Vaux and Castallo F. A. Davis Co.)

#### MANAGEMENT OF THE THIRD STAGE OF LABOR

Throughout the period of attending to the baby after its delivery, either the obstetrician or a competent assistant must make frequent observations of the condition of the uterus and the amount of bloody discharge from the vagina. Occasionally, partial detachment of the placenta will give rise to constant and severe vaginal bleeding, which necessitates the obstetrician's undivided attention.

The mechanism of separation of the placenta should not be rushed, but when the placenta has separated and lies in the lower segment of the uterus and in the vagina, its expulsion may be accelerated. The separation of the placenta can be recognized by changes in the contour and the station of the fundus, bloody discharge from the vagina and advancement of the umbilical cord.

When these signs are present, the placenta may be expelled from the birth canal by exerting manual pressure backward against the contracted uterus. In other words, by using the contracted and empty

organ as a piston (Fig 195), the placenta is forced out of the lower birth canal. As the mass of the placenta is expelled from the vagina, it should be turned over and over so that the membranes are rolled into a rope and drawn down complete from the uterine cavity (Fig 196). Placenta and membranes are collected in a basin held beneath the vaginal outlet with one hand while the other remains free for exerting pressure on the fundus.

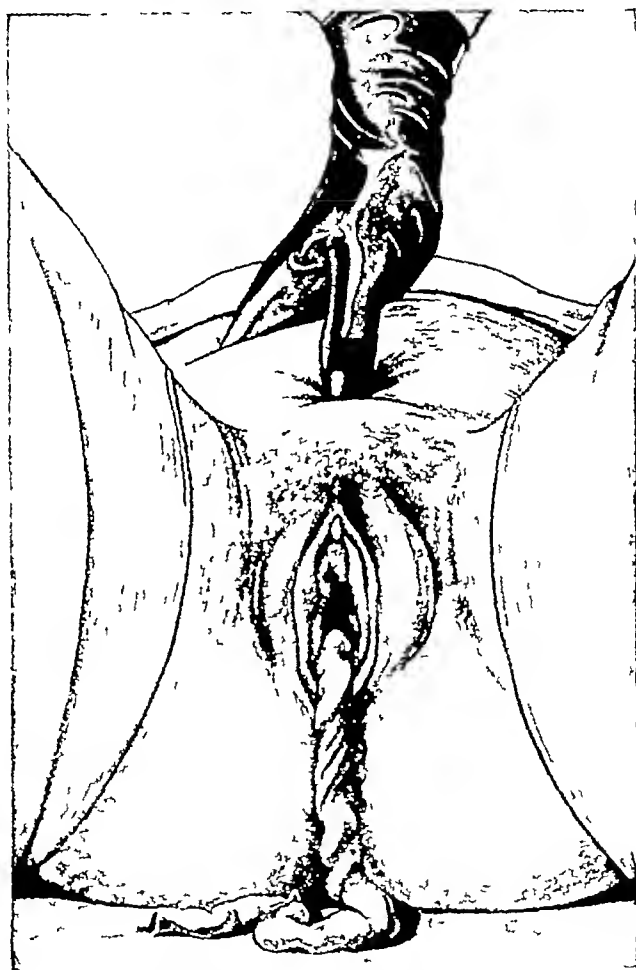


Fig 195—Expression of the placenta by pressure on the fundus ("Mechanics of Obstetrics" by Vaux and Castallo, F A Davis Co)

When the placenta has been delivered the hand of the obstetrician placed upon the maternal abdomen should follow the uterus down toward the pelvis and by vigorous massage insure that the uterus remains firmly contracted, thus avoiding excessive blood loss. This is followed by administering an oxytocic drug such as ergot, ergotrate or extract of posterior lobe pituitary or its derivatives.

**Inspection of the Placenta**—The next duty of the obstetrician is to examine the placenta and membranes to make sure that no portion is retained in the cavity of the uterus. This examination is accomplished by laying the placenta upon a table and carefully inspecting the maternal and fetal surfaces.

The maternal surface should present a composite and complete picture. The cotyledons should fit snugly against one another and the margin should be smoothly leveled off throughout the circumference. Upon the fetal surface the large branches of the umbilical vessels should be traceable to intact segments of the placental tissues. A large vessel torn off at the margin of the placenta or one which leads beyond the margin to a raw area on the membranes, indicates that a

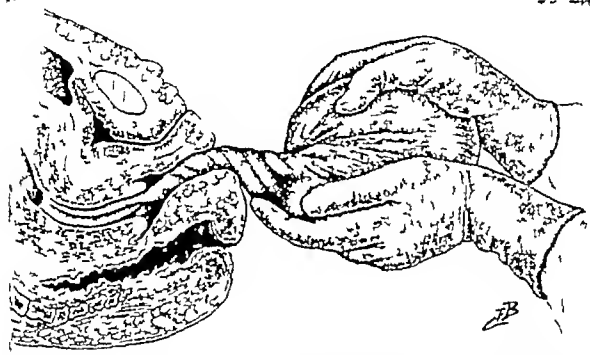


Fig 196—Method of extracting the membranes by rotating the placenta. ('Mechanics of Obstetrics' by Vaux and Castallo F. A. Davis Co.)

placenta "succenturiata" has been detached and retained in the uterine cavity.

The membranes should be examined to see if they are complete. Retention of membranes generally does no harm. Retained portions of placenta, however, should be removed, for they will give rise to postpartum hemorrhage and puerperal infections.

**Inspection for Lacerations**—After the operator is sure that the expulsion of the placenta is complete, the lower birth canal is examined for laceration. If labor has been spontaneous and uncomplicated, the cervix should not be inspected. If there are any lacerations of the perineum they should be immediately repaired unless the condition of the patient contraindicates anesthesia and manipulation.

## ANALGESIA AND ANESTHESIA, FORCEPS

**Analgesia**—The following analgesics may be used at home demerol, 100 mg, and  $\frac{1}{150}$  grain of scopolamine intramuscularly when the patient is having labor pains every three to five minutes lasting twenty to thirty seconds. If after one or two hours the analgesic effects appear to be wearing off, another dose of 100 mg of demerol intramuscularly is given. The scopolamine is repeated with demerol at four-hour intervals, but each subsequent dose of scopolamine is half of the previous dose. There is usually much relief of pain and partial amnesia. The patient will sleep between pains.

Another satisfactory analgesic agent is the combination of 3 grains of seconal by mouth and 1 gram of codeine sulfate intramuscularly. This combination usually gives good results with multiparous patients. If the patient develops hallucinations or excitability from either combination, open drop ether can be used to control her until she can be given rectal ether.

If neither of the above combinations gives good results, rectal ether may be employed. First a cleansing enema is given, then a rectal tube is passed to a point above the presenting part, if the presenting part is low. Two ounces of warm mineral oil is then instilled to protect the rectal mucosa, and this is followed by 2 ounces of ether. Finally 2 ounces of warm mineral oil is instilled to clear the rectal tube. The tube is removed and the gluteal cheeks are held together to aid the patient in retaining the enema. When ether is detectable on the breath of the patient it is a sign that the ether has been absorbed and the patient most likely will not expel the mixture. The results with rectal ether following one of the above combinations or as the sole agent are very often satisfactory.

**Anesthesia**—The only safe anesthetic for use at home is dropped ether. It is easily administered by anyone and the doctor can watch the effects as he is doing the delivery. Spinal and caudal anesthesia are contraindicated for use in home deliveries.

**Forceps**—The use of inlet or midplane forceps is a procedure for hospitals where there are proper supervision and facilities for the handling of any emergencies that might arise. There is no contraindication to the use of outlet forceps in the home if the doctor knows the indications and contraindications therefor.

## COMPLICATIONS OF LABOR

**Abnormal Presentations**—Whenever the doctor suspects or diagnoses an abnormal presentation such as breech, transverse lie or disproportion, the patient is admitted to the hospital. Good prenatal care and adequate attention to the patient during the early stages of labor will create opportunities for diagnosing the condition in time to get the patient to the hospital for the delivery.

**Postpartum Hemorrhage**—This complication is not common in our home deliveries. If excess bleeding is noticed, Credé's method is employed if the placenta has not been expelled. The uterus is lifted out of the pelvis. One hand placed above the symphysis pubis applies pressure towards the promontory of the sacrum and the other hand on the fundus applies pressure toward the symphysis. This brings the uterus under control while active measures are being provided.

Pituitrin and ergotamine tartrate are given intramuscularly. Then one ampule of ergotamine tartrate is given intravenously. The ambulance is sent with blood plasma, which the patient receives. The uterus is packed if it has not responded to oxytocic drugs. The patient is removed to the hospital, where further treatment for hemorrhage is administered.

**Infections.**—Some patients will be found with a septic temperature, due to the fact that they have had intercourse the night before going into labor. A mild *endometritis* develops. The endometritis at times becomes more severe. The patient develops a painful uterus and tenderness in the lower abdominal quadrants. Parametritis or pelvic cellulitis may develop. This condition responds favorably to sulfa therapy. The patient receives 2 gr of sulfadiazine or sulfathiazole, then 1 gm every four hours with equal amounts of sodium bicarbonate. Penicillin, 100,000 to 200,000 Oxford units per twenty-four hours, is also given in combination with sulfa therapy, depending upon the severity of the infection. Fluids are forced to over 2000 cc each twenty-four hours. A blood specimen and a catheterized specimen of urine are taken and examined at the hospital.

**Breast infections** are treated immediately by resting the breast, and early sulfa therapy is instituted. If an abscess forms, the patient is admitted to the hospital and the abscess is incised and drained.

**Pyelitis** is another common infection which responds very well to sulfa therapy.

**Breast infections** are treated immediately by resting the breast, and patients who live in poorly heated homes and whose surroundings are not the best. The patient is placed on 4 gm of sulfadiazine as the initial dose, then 1 gm every four hours with equal amounts of sodium bicarbonate. Fluids are forced to at least 2000 cc for every twenty-four hours. If the patient does not respond to sulfadiazine, penicillin therapy is instituted. A blood count and an examination of a catheterized specimen of urine are made every forty-eight hours when sulfonamides are given.

#### REFERENCE

- Vaux, N. W. and Castallo, N. A. *The Mechanics of Obstetrics*. Philadelphia, F. A. Davis Co., 1943.

## SINGLE DOSE AND CONTINUOUS SPINAL ANESTHESIA FOR LABOR AND VAGINAL DELIVERY

MAHLON C HINEBAUGH, JR., M.D.\* AND WARREN R LANG, M.D.†

SPINAL anesthesia was introduced in obstetrics by Kreis in 1900. Unfortunately, at this time cocaine was the only available anesthetic agent. Because of the marked toxicity of the drug, maternal mortality was high. As a result, the procedure met almost universal condemnation by the profession and it was soon abandoned. After a lapse of approximately twenty-five years interest in the method was revived. This was largely due to the development of new and less toxic drugs plus a more complete understanding of the physiology of spinal anesthesia and its mode of action. In 1930 Cosgrove<sup>1</sup> reported the first large series of cases delivered under spinal anesthesia. He was able to demonstrate that, when properly used, this type of anesthesia was relatively safe. Despite this favorable report, the reaction was by no means enthusiastic. The procedure continued to meet with violent opposition from many prominent obstetricians of the time. Its employment therefore continued to be restricted. During the period of 1930 to 1940 the use of spinal anesthesia for caesarean section became more widespread as its superiority over inhalation anesthetics became apparent. The introduction of continuous spinal anesthesia in 1940 by Lemmon<sup>2</sup> is to a considerable degree responsible for its present popularity.

### ADVANTAGES AND DISADVANTAGES

A discussion of the advantages and disadvantages of any obstetrical anesthesia should be based on (1) safety to the mother, (2) safety to the infant, (3) its effectiveness and (4) ease of administration.

Spinal anesthesia is essentially a form of local nerve block. Its effectiveness depends upon the paralysis of sensory nerve impulses as they enter the spinal cord. The fact that the action of spinal anesthesia is limited anatomically is of prime importance in the consideration of its application to obstetrics. Briefly, this anatomic limitation is dependent upon such factors as the site of injection, the amount, concentration and specific gravity of the agent, position of the patient, and barbotage. It is therefore possible to block the sensory innervation of the uterus ( $D_{11}$ ,  $D_{12}$ ), cervix and lower birth canal ( $S_2$ ,  $S_3$ ,  $S_4$ ), without producing paralysis of the motor fibers ( $D_6$  and above). This permits uterine contractions to continue and at the same time afford

\* Diplomate, American Board of Obstetrics and Gynecology, Demonstrator of Obstetrics, Jefferson Medical College, Assistant Obstetrician, Jefferson Medical College Hospital, Philadelphia

† Resident in Obstetrics and Gynecology, Jefferson Medical College Hospital

complete pain relief without materially interfering with the progress of labor. In addition, since the uterus retains its ability to contract firmly, the danger of atonic postpartum hemorrhage is greatly reduced. The complete relaxation of the pelvic floor and perineum incident to spinal anesthesia greatly facilitates certain operative procedures such as midforceps rotation and extraction.

Of considerable importance is the ability of the completely conscious patient to cooperate. Indeed, in a multipara painless spontaneous delivery can be accomplished by instructing her to "bear down" during the uterine contractions. Furthermore, there is no need to restrict fluids or food in the immediate postpartum period. This is in marked contrast to inhalation anesthetics. Throughout our experience with spinal anesthesia, particularly when using the continuous technic, we have been impressed by the fact that practically every woman is conscious of a deep emotional satisfaction in being awake during her delivery and seeing her child as soon as it is born. This accounts in a large measure for the marked enthusiasm of the patient for this method of pain relief. Of almost equal importance to the welfare of the mother is the necessity for safeguarding the infant. In this respect spinal anesthesia is unique. As we and others have pointed out in previous papers, spinal and continuous spinal anesthesia are without any adverse effect upon the fetus.<sup>2,4</sup> Respiration is immediately established and cyanosis is absent.

In the main, the disadvantages of spinal anesthesia are minor in character. Those antagonistic to its use attempt to justify their position by simply stating that it is too dangerous for the pregnant woman. Careful analysis fails to substantiate this claim. For the most part, fatalities are due to such avoidable factors as (1) its selection in spite of contraindications, (2) errors in technic, and (3) its employment by unqualified individuals. In this connection it seems rather strange that physicians who would never think of administering chloroform or nitrous oxide to a patient will without any hesitation attempt to give a spinal anesthetic. Probably the greatest single disadvantage to spinal anesthesia is its limitation of applicability. It should never be used except in a well equipped institution and under the direction of a well trained anesthetist. Oxygen, vasopressor drugs, stimulants and intravenous fluids must be available for immediate use. Because of the high incidence of operative delivery spinal anesthesia is not suited for the untrained obstetrician. A small percentage of patients complain of headache following delivery, but this is in most instances readily controlled by ergotamine tartrate and aspirin.

#### INDICATIONS AND CONTRAINDICATIONS

Because its effect is restricted to a local area, spinal anesthesia is particularly indicated in the following conditions: (1) infections of the respiratory tract, whether acute or chronic; (2) certain types of heart



disease, (3) hypertensive toxemia, because of the reduction of blood pressure and vasodilatation resulting in increased urinary output, (4) prematurity, (5) previous cervical and vaginal plastics due to its relaxing effect on the lower genital tract

Spinal anesthesia is contraindicated in (1) severe anemia (vasodilatation of the lower extremities in the presence of decreased blood volume predisposes to anoxemia), (2) marked deformity of the spinal canal or disease of the spinal cord, (3) local infections at or near the site of injection, (4) marked obesity, (5) those emotionally unsuited, (6) when there is a history of sensitivity to the drug

Obstetrical contraindications pertinent to vaginal delivery are (1) placenta praevia (the relaxing effect of spinal anesthesia on the lower uterine segment may cause marked bleeding), (2) cephalo-pelvic disproportion, (3) nonengagement of the presenting part, (4) in the presence of known fetal deformity or intrauterine fetal death, (5) such operative procedures as internal podalic version and certain cases of breech decomposition and extraction

#### SINGLE DOSE SPINAL ANESTHESIA

Single dose spinal anesthesia has been employed with increasing frequency during the past ten years. Its use is restricted by virtue of the fact that there is a definite limitation of the duration of anesthesia. There is some variation in the duration of anesthesia dependent upon the anesthetic agent employed. At the present time there are three drugs in common use.

*Procaine hydrochloride* (novocaine) is more extensively used than any other local anesthetic and has survived the test of clinical trial. Its toxicity is approximately one-sixth that of cocaine. The injection of 50 mg, dissolved in 2 cc of spinal fluid, is usually sufficient to produce good relaxation. The average duration of anesthesia is forty minutes.

*Pontocaine*, a very popular anesthetic in general surgery, has a limited number of advocates for vaginal delivery. It produces a prolonged anesthesia which is advantageous. However, this advantage is more than offset by the fact that it is eight times as toxic as procaine. In our opinion this high toxicity unnecessarily increases the danger to the patient and we do not recommend it. For those who wish to employ this drug we suggest the administration of 5 mg dissolved in 10 per cent glucose.

*Metycaine hydrochloride* is in our experience the drug of choice. It possesses a low toxicity, is prompt and uniform in action, and relatively long lasting in its effect.<sup>5</sup> We employ 1.5 per cent metycaine in Ringer's solution (15 mg/cc). The average dose is 30 to 45 mg or approximately three-fourths the dose of procaine.

The injection of any anesthetic agent into the subarachnoid space may produce systemic toxic effects. The most important of these toxic

reactions are (1) central nervous system excitation, (2) cardiorespiratory failure, (3) allergic phenomena, (4) a combination of several factors. Despite the fact that allergic reactions are rare, it is wise to question patients with regard to a history of sensitivity to local anesthesia. Skin reactions have been recommended but are probably of little value.

**Technic.**—There are certain prerequisites for the safe administration of single dose spinal anesthesia. In a nullipara, the cervix must be completely dilated and the presenting part at the level with the ischial spines or below. In other words, it should not be given until the patient is ready for delivery. In a multipara the anesthesia may be induced before the cervix is completely dilated if the patient is having second stage pains and the presenting part is in the midpelvis. When these conditions have been satisfied, the patient is removed to the delivery room. Her pulse and blood pressure are recorded. If these are within normal limits she is placed on either side in an attitude of complete flexion suitable for lumbar puncture. After thorough surgical preparation of the area, the skin overlying the third or fourth lumbar interspace is infiltrated with local anesthesia. This may be accomplished by using procaine ephedrine solution (1 cc ampule) or metycaine. The wheal should be small in order to avoid obliteration of the landmarks. A small gauge spinal needle (No. 22) is then inserted into the chosen interspace and a free drip of spinal fluid is obtained. If procaine hydrochloride is used, 2 cc. of spinal fluid are withdrawn in which to dissolve 50 mg. of the drug. When metycaine (1.5 per cent in Ringer's solution) is used there is no need to withdraw spinal fluid. The anesthetic is slowly injected without barbotage and the needle removed.

The patient is now placed in the lithotomy position and prepared for delivery. The pulse and blood pressure are checked at five-minute intervals during the first half hour and then every ten to fifteen minutes until she has completely reacted from the anesthesia. Should the systolic pressure fall below 90 mm. a vasopressor drug, such as ephedrine sulfate, grain  $\frac{3}{4}$ , is administered hypodermically. Throughout the actual delivery 100 per cent oxygen is given by mask. We wish to emphasize the use of oxygen during the delivery. It acts to prevent any material drop in blood pressure and offset any tendency of the anesthesia to produce cardiorespiratory depression.

**CASE HISTORY.**—Mrs. D. McK., white, aged 26 years, Para O. Gravid 1, was referred from the medical department for antenatal care and delivery. She had been under collapse therapy for pulmonary tuberculosis for the past two years. Antenatal course was uneventful. The onset of labor was at 10 A.M. with premature rupture of membranes. She was admitted to the hospital at 4 P.M. not in labor. Uterine contractions began at 8.30 P.M. Examination at this time revealed longitudinal lie, back to right, vertex presenting. FHS 136 R/L toward flank, cervix unaffected and undilated, presenting part at ischial spines. Four hours later the

patient was quite active and labor was progressing normally Analgesia was secured by seconal, grains 3, and hyoscine, grain 1/150

At 7 A M on the following day the cervix was completely dilated, head station midpelvis, position ROT Because of the pulmonary complication it was deemed advisable to shorten the second stage and the patient was removed to the delivery room Fifty milligrams of procaine hydrochloride was injected through the third lumbar interspace The patient was prepared for delivery Vaginal examination verified the position Apparently as a result of relaxation incident to the spinal anesthesia plus continuation of uterine contractions, the head descended to the pelvic floor Delivery was accomplished by an easy rotation and extraction A wide mediolateral episiotomy was done because of the large head Following birth of the child the uterus contracted firmly with very slight blood loss The placenta separated almost immediately and was expressed by simple fundal pressure at the end of three minutes, following which the uterus again contracted firmly with the blood loss minimal

The patient reacted well following delivery, artificial pneumothorax was repeated on the first postpartum day and the patient's hospital course was entirely normal The labor and delivery were without adverse effect upon the pulmonary lesion

#### CONTINUOUS SPINAL ANESTHESIA

Continuous spinal anesthesia for labor and vaginal delivery was first instituted, to our knowledge, by one of us in January, 1944 Our investigation was initiated through a desire to avoid certain disadvantages of continuous caudal analgesia as described by Hingson and Edwards<sup>6</sup> These disadvantages while primarily technical, are nevertheless of great importance clinically (1) It is more difficult to insert a needle properly into the caudal canal than to perform a successful lumbar puncture, (2) massive doses of anesthetic solution are necessary in caudal analgesia, whereas in continuous spinal one-twentieth to one-thirtieth of that dose produces the equivalent effect, (3) the danger of the inadvertent introduction of the needle into the sub-arachnoid space or a vein during caudal analgesia is ever present, (4) should any toxic reaction occur during caudal analgesia, the anesthetic cannot be withdrawn In all other respects the factors which govern the use of continuous caudal analgesia apply to continuous spinal anesthesia By virtue of the small dosage requirement of the latter, it is possible to produce analgesia (sensory loss without motor paralysis) during the later part of the first stage of labor and anesthesia during the second stage for delivery Throughout our experience with this method of pain relief, we have constantly endeavored to improve and simplify the technic We believe that our present method is the nearest approach to an ideal obstetrical anesthetic It provides complete pain relief without jeopardizing the welfare of mother or child<sup>3</sup>

Since continuous spinal anesthesia is instituted during the first stage of labor, the following requirements must be fulfilled (1) the patient must be in active labor and have reached a point where she is suffering severe pain, (2) the presenting part must be at a level with or below the ischial spines, (3) in a nullipara the cervix should be dilated

at least 6 cm., but 4 cm. is sufficient in a multipara. Failure to satisfy these requirements can only result in prolongation or actual cessation of labor.

**Technic**—Continuous spinal anesthesia may be induced in either the labor or delivery room, depending upon individual preference. The patient is prepared for lumbar puncture following the technic used for single dose spinal anesthesia. We prefer the second or third lumbar interspace. A 25 or 3 inch malleable caudal needle, of the type used by Hingson and Edwards,<sup>6</sup> is inserted into the chosen interspace and a free drip of spinal fluid is obtained. The back is then extended in order to fix the needle firmly. The needle is then connected by rubber tubing to a 10 cc. Luer-Lok syringe with cut-off valve containing 15 per cent metycaine in Ringer's solution. An initial dose of 15 mg. (1 cc.) is slowly injected without barbotage. This dose is in most instances sufficient to produce complete relief of pain within five minutes. Additional injections of 15 mg. are repeated at necessary intervals, usually thirty to forty minutes, to maintain analgesia.

For best results it is advisable to use a split mattress and place the patient on her back after the initial injection. This affords greater comfort to the patient and produces equal distribution of anesthesia. If a split mattress is not available the patient must remain on her side. In case of unilateral anesthesia turning the patient on the opposite side gives prompt relief.

The level of anesthesia is checked at frequent intervals and should not extend more than 2 or 3 cm. above the umbilicus. Should the anesthesia level reach the xiphoid or above, paralysis of the motor fibers of the uterus will result in cessation of labor. The pulse, blood pressure and respirations are carefully watched throughout the duration of the anesthesia. The progress of labor is determined by the frequency, force and duration of uterine contractions, increase in cervical dilatation and descent of the presenting part. We rely on rectal examinations. The delivery is conducted in the usual manner. We routinely use outlet forceps combined with episiotomy. The third stage of labor is allowed to occur normally. In most instances the placenta separates promptly and may be expressed by simple fundal pressure within five minutes.

Following completion of the third stage 1 cc. of pituitrin is administered. Under no circumstances should an oxytocic be given before removal of the placenta. Failure to observe this precaution will result in retention of the placenta for a number of hours. It must be remembered that spinal anesthesia does not interfere with the ability of the uterus to contract. Repair of the episiotomy is then carried out. We have noted a slight increase in the amount of bleeding from the incised perineum. This is due to vasodilatation incident to spinal anesthesia. The needle is not removed until repair of the episiotomy has been completed. If desired, prompt restoration of sensation may be

established by withdrawing a small amount of spinal fluid containing the anesthetic solution

**CASE HISTORY**—E. P., white, aged 27 years, Para O Gravida I Antepartum course was normal until the thirty-second week, at which time she developed hypertension (140/90), albuminuria and edema. She was admitted to the hospital. Her toxemia was brought under control and she was discharged at the end of one week with the diagnosis of mild preeclampsia. She was readmitted in active labor at 1:30 P.M. On admission the blood pressure was 140/90, no edema was present and the urine showed a plus 1 albumin. Uterine contractions were recurring at five-minute intervals, duration forty seconds, back to left, FHS 140 11q, cervix completely effaced and 2 cm dilated, vertex presenting, station midpelvis, position LOA. To secure preliminary analgesia, demerol 100 mg intravenously and scopolamine grain 1/150 intramuscularly were administered with good effect.

At 12:30 A.M. on the following day the cervix was 6 cm dilated, head station unchanged, uterine contractions every three minutes, duration fifty seconds. Continuous spinal anesthesia was induced with metycaïne, the initial dose being 15 mg. During the next two hours, the patient experienced no pain. There was a gradual drop in blood pressure to 120/80. At 2:30 A.M. rectal examination revealed complete cervical dilatation with head on the pelvic floor. Up to the time of delivery a total of 60 mg of metycaïne was injected. The delivery was completed by outlet forceps with a left mediolateral episiotomy.

Following delivery of the child the uterus contracted firmly. The placenta separated promptly and was expressed at the end of five minutes by simple fundal pressure. The uterus again contracted firmly and blood loss was minimal. The infant cried immediately and there was no cyanosis. Primary repair of the episiotomy was then carried out. The puerperal course was entirely normal and the patient was discharged on the tenth postpartum day.

### SUMMARY

There are certain disadvantages of single dose spinal anesthesia which are overcome by the use of the continuous technic. These disadvantages are, as pointed out by Lemmon<sup>7</sup> (1) failure of the single dose to produce the level and degree of anesthesia desired, (2) failure of the anesthesia to last for the length of time required to perform the procedure, (3) the inability to remove the anesthetic agent should any toxic reaction occur. The ability to immediately withdraw spinal fluid containing the anesthetic solution in the event of any toxic symptoms affords a safety factor which is of vital importance. An evaluation of the two technics, based upon extensive experience with each, leaves no doubt in our minds as to the overwhelming superiority of the continuous method. The administration of any anesthetic for delivery involves a certain element of risk. We firmly believe that continuous spinal, properly used, affords greater safety to both mother and child than any other method at the present time. Finally, it seems to us unnecessary to produce a general state of anesthesia when only local analgesia is required.

## BIBLIOGRAPHY

- 1 Cosgrove, C. S. *Anesth & Analg.*, 9 71-76, 1930
- 2 Lemmon, W. T. A Method for Continuous Spinal Anesthesia. *Ann. Surg.*, 11 141 1940
- 3 Hinebaugh, M. C., Jr and Lang, W. R. Continuous Spinal Anesthesia for Labor and Delivery *Ann. Surg.*, 120 143, 1944
- 4 Lull, C. B and Hingson, R. A. *Control of Pain in Childbirth*. Philadelphia, J B Lippincott Co., 1940
- 5 Woodbridge, P. D. Metycaine Spinal Anesthesia Report of 1381 Cases. *Am. J Surg.*, 37 191, 1937
- 6 Hingson, R. A. and Edwards, W. B. Continuous Caudal Anesthesia in Obstetrics *Am J Surg.*, 57-459 1942
- 7 Lemmon, W. T and Hager H. G. Continuous Spinal Anesthesia. *Ann. Surg.*, 120 129 1944

## SOME RECENT LABORATORY PROCEDURES OF IMPORTANCE IN OBSTETRICS AND GYNECOLOGY

(Rh Test; Vaginal Smears for Ovarian Function and Uterine  
Cancer; New Tests for Pregnancy)

A. E. RAKOFF, M.D.\*

### THE RH FACTOR

ALTHOUGH the discovery of the Rh factor<sup>1</sup> is only five years old it has assumed a place of considerable importance in obstetric practice not only because of its significance in relationship to erythroblastosis foetalis and transfusion reactions<sup>2</sup> but because abnormalities in this factor can *potentially* involve up to 15 per cent of pregnancies.

The Rh factor is an antigenic substance commonly present in human red cells specifically distinct from the major blood factors, A and B, and also from the subtypes such M, N and P. The Rh agglutinin has also the property of greater activity at 37° C. than at lower temperatures and is therefore termed a "warm" agglutinin.

Individuals in whom this Rh agglutinin or factor is present are designated as "Rh positive" while those in whom it is absent are called "Rh negative." An Rh-negative individual can be stimulated to produce "Rh antibodies" (anti-Rh agglutinins) by the injection of Rh-positive red cells, such as may occur by blood transfusion or passage of Rh-positive red cells from the fetal circulation to the maternal circulation during pregnancy. In the latter event "isoimmunization" of the mother may occur. The anti-Rh agglutinins are present in the serum and may pass from the maternal circulation through the placenta to the fetus, destroying the fetal red cells and producing hemolytic anemia with its sequelae, erythroblastemia, jaundice and edema, giving rise to the various clinical manifestations of fetal erythroblastosis.

The Rh factor is inherited as a simple mendelian dominant characteristic independently of the major blood groups and the M-N types.<sup>3</sup> By means of different anti-Rh sera it is now recognized that the Rh factor is antigenically and genetically complex, probably being carried by a series of allelic genes variously designated by different serologists.<sup>4</sup> However, as pointed out by Levine,<sup>5</sup> since 92 per cent of all Rh incompatibilities in the mothers of erythroblastotic infants can be

---

From the Departments of Obstetrics and Gynecology, the Endocrine Laboratory and Clinic, Jefferson Medical College and Hospital, Philadelphia.

\* Director of the Endocrine Laboratory, Jefferson Hospital, Instructor in Gynecology, Assistant Demonstrator in Obstetrics, Jefferson Medical College.

detected with a single anti-Rh serum (anti-Rho), for usual clinical purposes one may recommend the simple genetic theory based on but a single antibody. The finer differences of the Rh factor and the rare instances of isoimmunization with other factors are best left to the serologic specialist.

It has been found by sampling of various population groups that approximately 85 per cent of all white women are Rh positive and 15 per cent are Rh negative. Among Negroes 5 per cent are found to be Rh negative, and only 1 per cent among the Chinese.<sup>6</sup> Because of the high incidence of Rh-negative individuals, particularly in the white population routine "Rh testing" of prospective mothers has become the rule in many institutions. Since immunization may occur in women following transfusions, Rh testing has also been recommended before transfusing young girls and women in the childbearing period.

**Test for Rh Typing**—A satisfactory technic<sup>\*</sup> is as follows

- In a carefully cleaned small test tube (about 0.4×8 cm.)
  1. Wash cells three times with saline.
  2. Place 2 drops of anti Rh serum.
  3. Add 2 drops of fresh saline suspension (2 per cent) of red cells to be tested (This corresponds in color to that obtained by the addition of one drop of blood to 2 cc. of saline)
  4. Shake and place in water bath at 37° C for thirty minutes.
  5. Centrifuge for one minute at 400 R.P.M. and observe sedimented blood and shake gently
  6. Inspect grossly for clumping. Those clumped are Rh positive.
  7. Inspect microscopically (low power) all grossly negative. Only those negative microscopically are considered Rh negative. (A small drop for microscopic inspection may be easily removed from the test tube to a microscopic slide by means of a small glass rod)
  8. In all questionable instances check on original saline suspension of unknown cells be sure that these are even unagglutinated suspensions of red cells

In the event that a prospective mother is found to be Rh negative it becomes necessary to test her husband. If he is found to be Rh positive the potentiality of an Rh incompatibility arises, whereas if he is Rh negative no such difficulty will ordinarily occur since the fetus will be Rh negative. Although 12 to 13 per cent of all matings will be between Rh negative women and Rh positive men, fortunately only a small percentage of them will result in fetal erythroblastosis (0.1 per cent of all pregnancies) because of the following factors<sup>7</sup>

1. In those instances in which the Rh-positive father is heterozygous (i.e., he carries an Rh positive gene and an Rh negative gene) 50 per cent of the babies will be Rh negative. In certain cases it is possible for the serologic specialist to determine whether a given individual is homozygous or heterozygous particularly by means of still another recently discovered blood factor the Hr factor. It has been shown that individuals whose blood is Hr negative are homozygous for the Rh factor at least so far as the clinical results are concerned.<sup>8</sup>

Technic employed by Dr. Lowell Erf, Hematology Division, Jefferson Hospital Philadelphia.



2 Where an Rh incompatibility exists, the first pregnancy frequently escapes or the erythroblastosis is not severe because the process of immunization requires time to develop. If the patient has been "sensitized" by a previous transfusion of Rh positive blood the mechanism may operate at once. Repeated transfusions of Rh positive blood may give rise to a "transfusion" reaction, explaining many hitherto puzzling transfusion reactions.

3 Although one in seven individuals is Rh negative, according to Wiener only about one in fifty of these is readily sensitized.

4 Occasionally a normal fetus is born despite active isoimmunization of the mother as indicated by the presence of a high titer of Rh agglutinins in her blood. On the other hand, Levine<sup>5</sup> states that in 8 per cent of erythroblastotic infants the mothers are Rh positive but isoimmunization may have resulted from (a) finer differences in the Rh factor, (b) properties A or B of fetal blood, (c) nonsecretory type, or (d) Hr factor.

In pregnancies of Rh-negative women married to Rh-positive husbands, testing the maternal blood at intervals throughout gestation for Rh antibodies is a helpful procedure in determining whether isoimmunization is occurring. In this agglutination reaction, the maternal serum is used as the testing serum against known suspension of Rh-positive red cells. By using various dilutions of maternal serum the "titer" of the Rh antibodies can be determined. In Rh negative women who have been pregnant before or previously transfused, it is wise to test for antibodies before the onset of pregnancy, since such antibodies may persist for a considerable time. An increasing antibody titer as pregnancy progresses usually indicates active isoimmunization and usually indicates an unfavorable prognosis. If the fetus reaches viability, interruption of the pregnancy in an attempt to obtain a live baby is sometimes advocated. All preparations should be made to transfuse the baby at once with Rh-negative blood free of Rh antibodies. Blood from the mother should *never* be used.

Wiener has recently pointed out that in some instances Rh antibodies cannot be demonstrated by the usual agglutination reaction because they are present in a "blocked" form. He has described a "blocking test" by which these antibodies can be demonstrated.<sup>8</sup>

It is generally agreed that Rh incompatibility is not an important cause of habitual abortion and miscarriage but that it becomes a factor only in the latter half of pregnancy.

## CYTOLOGY OF VAGINAL SMEARS

(With Particular Reference to Ovarian Function and Uterine Cancer)

Examination of the cells found in vaginal smears has become one of the most useful laboratory procedures for the gynecologist. Many years of persistent study of human vaginal cytology by Papanicolaou and more recently by others have shown that much can be learned concerning ovarian function, tumors and other diseases of the genital tract by examining the cells which have been shed from the genital tract and have collected in the vagina. Indeed, it would seem that ade-

quate examination of such smears bears the same diagnostic significance in regard to the genital tract as does the routine urinalysis to the urinary tract

So far as ovarian function is concerned, the staining procedure and the examination of the smear can be simplified to take but a few minutes for each slide, and even the novice can quickly learn to interpret the more significant findings. On the other hand, the preparation of smears for the diagnosis of uterine cancer requires much more detailed technic. Furthermore, the proper interpretation of such smears requires a considerable experience in recognizing the many types of cells which can be found in even normal women, their site of origin, the less common cells found in various functional and benign lesions of the genital tract, as well as the characteristics of cells that arise from malignant lesions. It is gratifying, however, that the more time one devotes to the study of these smears, the more fruitful become the results of each succeeding examination.

**Preparation of Vaginal Smears.**—It is preferable that the patient does not douche on the day on which the smear is to be taken. A slightly curved glass pipette, 6 to 8 inches in length and about 0.5 cm. in diameter, with a rounded narrow tip and attached to a strong rubber bulb of 1 or 2 ounce capacity, for producing suction, is used for collecting the secretion. The rubber bulb is compressed, the glass pipette is introduced into the posterior fornix of the vagina and the vaginal secretion is sucked into the pipette. The tip of the tube is moved from one side of the fornix to the other so that all parts are sampled. The material thus collected is blown on the surface of a clean microscope slide and further spread with the convex side of the pipette. *Before the smear can dry* the slide is immediately dropped into a Coplin jar containing equal parts of 95 per cent alcohol and ether. Although fixation does not require more than a few minutes, the slides may be kept in the fixative, without harm, for as long as a week.

**Staining Vaginal Smears.**—1 *For Ovarian Function.*—Smears that are to be examined only for ovarian function can be stained by a simplified procedure using prepared differential stains such as suggested by Papanicolaou<sup>9</sup> or Shorr<sup>10</sup>.

The Shorr stain (S3) has the following formula

Biebrich Scarlet (water sol.)	0.5	gm.
Orange G	9.25	gm.
Fast Green FCF	0.075	gm.
Aniline Blue (water sol.)	0.04	gm.
Phosphotungstic and Phosphomolybdic Acids CP	22 0.5	gm.
Glacial Acetic Acid	1.0	cc.
Dissolve all completely in 50 per cent ethyl alcohol	100	cc.

<sup>9</sup> Stain (EA50) can be obtained from Ortho Pharmaceutical Corp., Linden, New Jersey

<sup>10</sup> Single Differential Stain (Shorr) can be obtained from Wyeth Incorporated, Philadelphia.

The latter stain may be applied by dropper for one to two minutes, the slide is then dipped ten times in 70 per cent, 95 per cent and absolute alcohol (may be omitted by blotting after 95 per cent alcohol), well cleared in xylol and mounted

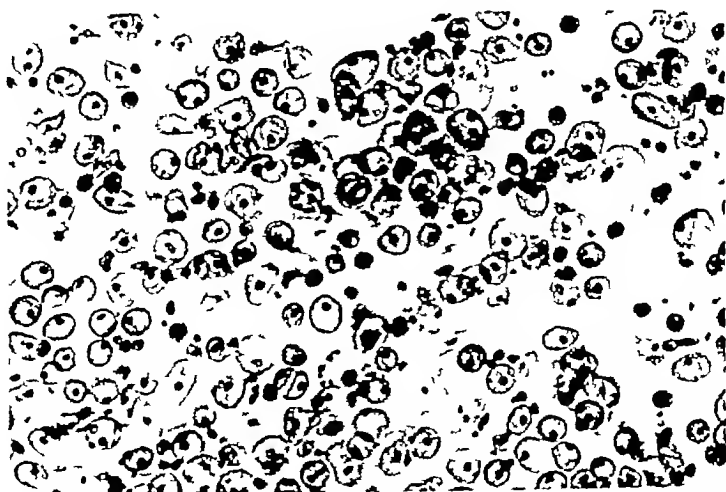


Fig 197—Vaginal smear from a menopausal woman showing marked estrogen deficiency as indicated by large numbers of small, round, green staining cells from the basal layer of the vagina



Fig 198—Vaginal smear from a young woman at the midcycle showing good estrogen effect as indicated by large squamous epithelial cells most of which are partially cornified and take an orange-red stain

The "atrophic cells," small in size, rounded in shape, take the lavender stain (Fig 197) Under estrogenic influence the larger squamous epithelial cells appear and are of green color, while with full cornification, the squamous cells assume a brilliant orange red hue (Fig 198) More detailed study of the morphology permits further evaluation of

the estrogenic effect. The experienced observer often can note changes in day to-day smears suggestive of corpus luteum function as well, although there are no specific criteria of progesterone function.

During pregnancy the cells tend to become elongated, concave or navicular, or totally vacuolized and the nucleus often elongated or collapsed.<sup>11</sup> Regression of these changes and the appearance of red cells is often noted in threatened abortion or impending parturition.

2 For the Diagnosis of Uterine Cancer—Papanicolaou has devised many stains and techniques to yield the excellent cytologic detail necessary for studying malignant cells. A very satisfactory procedure suggested by Papanicolaou<sup>6</sup> is as follows:

1 Fix smears before drying in equal parts of 95 per cent alcohol and ether for five minutes or longer. Rinse in 70 per cent and 50 per cent alcohols and in distilled water.

2. Stain in hematoxylin for five to ten minutes. Rinse three to four times in 0.5 per cent aqueous solution of HCl. Rinse thoroughly in water. Leave for one minute in a weak solution of lithium carbonate (3 drops of a saturated aqueous solution per 100 cc. of water). Rinse thoroughly in water.

3 Rinse in distilled water then in 50, 70, 80 and 95 per cent alcohols.

4 Stain for one minute in solution OG 6 consists of Orange G (National Aniline and Chemical Co.) 0.5 per cent solution in 95 per cent alcohol, 100 cc., and phosphotungstic 0.025 gm.

5 Rinse five to ten times in each of two jars containing 95 per cent alcohol to remove excess stain.

6 Stain for two minutes in EA36

Light Green (0.5 per cent solution in 95 per cent alcohol) 45 cc.

Bismarck Brown (0.5 per cent solution in 95 per cent alcohol) 10 cc.

Eosin Yellowish (0.5 per cent solution in 95 per cent alcohol) 45 cc.

Acid Phosphotungstic 0.200 gm.

Lithium Carbonate (Saturated Aqueous Solution) 1 drop

7 Rinse five to ten times in each of three jars containing 95 per cent alcohol. Rinse in absolute alcohol. Mount in Canada Balsam.

It has already been emphasized that it is necessary to be thoroughly familiar with the normal cells of the vaginal mucosa, cervix and endometrium before attempting to recognize the atypical malignant cells. Excellent descriptions and drawings can be found in the monograph by Papanicolaou and Traut.<sup>12</sup>

The diagnosis of carcinoma of the cervix depends upon finding atypical cervical cells in which there is great variation from the normal in size, shape and form and especially with abnormalities in the size, form and staining reaction of the nuclei (Figs. 199 and 200). Many varieties of abnormal and bizarre cells may be found depending upon the type of malignancy, degree of activity, degenerative changes and the like. Red blood cells or evidences of bleeding are almost invariably present and usually there are many leukocytes and histiocytes.

The diagnosis of endometrial carcinoma by the vaginal smear

method is much more difficult. The cells seen are much like those noted in sections of the tumor. The abnormal endometrial cells are on the average larger than the normal endometrial cells and also show greater variation in the size of the nuclei. The nuclei are usually hyperchromic, mitoses are not common.



Fig 199—A typical "tadpole" cell from a patient with cervical carcinoma. Note the bizzare shape of the cell and the abnormally large hyperchromic nucleus.



Fig 200—A group of cervical cancer cells of the "prickle cell" variety showing abnormality in size, shape and staining reaction with marked variation in the nuclei.

The value of the vaginal smear method as a diagnostic procedure to determine cancer remains to be determined. In the hands of experienced workers it appears to be of value as an aid in directing suspicion upon cases worthy of further investigation. It is not at present intended as a method for establishing an absolute diagnosis of cancer.

or for replacing biopsy, rather it aims to uncover cases which should be studied by biopsy. The most encouraging reports of all concern the cases in which "positive" smears were obtained in very early lesions which were missed on clinical study or even by biopsy<sup>12, 13</sup>

### TESTS FOR PREGNANCY

Of the various laboratory procedures which have been offered for the diagnosis of pregnancy, those based on the demonstration of a *high titer of chorionic gonadotropic hormone in the blood or urine* continue to be the most generally acceptable. In addition to the well established Aschheim-Zondek and Friedman tests, several other techniques based on this same principle have recently been described including the "frog test" and several rapid rat tests.

**South African Frog (*Xenopus laevis*) Test**—When the female South African frog (*Xenopus laevis*) is injected with chorionic gonadotropic hormone such as is present in the blood or urine of pregnant women, eggs are extruded within six to eighteen hours. This species of frog is peculiarly suited for this test in that it carries eggs in its abdomen throughout the year rather than only at mating time. The animals do not regularly react to small amounts of chorionic gonadotropin. The injection of larger amounts of hormone therefore requires initial concentration of the hormone in the urine specimen.

**Procedure**<sup>14</sup>—To 80 cc. of urine twice the volume of acetone is added. The mixture is thoroughly stirred and allowed to stand for fifteen minutes or longer to precipitate the proteins. The precipitate which contains the gonadotropic hormone is collected by decanting and centrifuging. The precipitate is allowed to dry. The hormone is then extracted by adding 2 or 3 cc. of distilled water, stirring thoroughly and centrifuging or filtering. One half of the recovered supernatant (representing 40 cc. of urine) is injected into the dorsal lymph sac space of the frog by means of a short needle. Care must be taken to avoid puncturing the lungs. It is preferable to inject two frogs for each test. Only mature, healthy, well nourished female animals should be used, preferably those which have reacted previously to chorionic gonadotropic substance. The animals may be used again after a week if the test is negative or after a month following a positive test. The animals are left in tanks at room temperature ( $70^{\circ}\text{F} \pm 5$ ) with water at a level of about 3 inches. They are fed small strips of beef heart or calves liver twice a week. Before testing they are placed in individual tanks fitted with a wire mesh platform to permit the extruded eggs to fall through without danger of the frog devouring the extruded eggs.

The advantage of the frog test, of course, is its rapidity, this makes it particularly useful in cases of suspected ectopic pregnancy and other surgical emergencies involving possible pregnancy. The ease with which the test is read is also of advantage. The chief disadvantage in our experience is that the animals sometimes become refractory and fail to respond to relatively large amounts of chorionic gonadotropic hormone, thus giving "false negative" tests. We have

never encountered a "false positive" The necessity for preliminary concentration of the urine is another disadvantage, as is also the present difficulty in obtaining the animals and their initial expense

**Rapid Rat Tests for Pregnancy**—The earliest reaction produced by chorionic gonadotropin in the rat ovary is a hyperemia which may appear within two to six hours and which has been used as the basis of a hormone test for pregnancy by a number of workers employing various technics

*Procedure*—Zondek and co-workers,<sup>15</sup> in a recent review of the subject, suggests that 2 cc of urine should be injected subcutaneously into infantile female rats (three to five weeks old) in two injections of 2 cc each at an interval of one hour One rat is killed after six hours and the other two are killed in twenty-four hours, preferably with illuminating gas The reaction is positive if hyperemia (nearly "strawberry red" color) appears in at least one ovary of two different rats For the beginner, noninjected rats should be used as a control Zondek found that reading the test at two hours gave a 15 per cent error, at six hours a 78 per cent error, while at twenty-four hours there was a 1 per cent error (all false positives)

In our own experience with the hyperemia tests, we have not been highly successful There was frequently a difference of opinion in the laboratory as to whether the ovaries of a given test were sufficiently pink to constitute a positive test Differences in the age and strain of animals were also found to be important factors in the reliability of the reaction

**"Chemical Tests" for Pregnancy**—Unfortunately no suitable color reaction or other chemical test which is specific for chorionic gonadotropin has been discovered Tests for other substances in the urine of pregnancy have been described from time to time but have not proved to be generally satisfactory because they lack specificity Except for chorionic gonadotropin, there is no other known substance which is specifically produced in large amounts in early pregnancy

Recently Guterman<sup>16</sup> has described a simplified color reaction for pregnandiol in the urine as a diagnostic procedure for pregnancy The test is based on the principle that if pregnandiol is present in an amenorrheic patient, pregnancy is possible

The method, which is too lengthy to be given in detail here, consists essentially of the extraction with toluene of the acid-hydrolyzed pregnandiol complex of urine, followed by the purification and precipitation of the pregnandiol The characteristic orange to orange-brown color is developed by sulfuric acid Four to six such tests can be run simultaneously by one person in three hours

In our experience, pregnandiol color reactions, although considerably better than other chemical tests for pregnancy, have not proved sufficiently accurate to compare favorably with the Friedman or Aschheim-Zondek procedures In early pregnancy the pregnandiol concentration is sometimes not sufficiently high to be readily demon-

strable by the method described, on the other hand, in some instances of delayed menstruation, pregnandiol or pregnandiol-like substances have been present in sufficient amounts to give false positive reaction.

Chemical tests based on the demonstration of increased titers of estrogens, as an indicator of pregnancy, are not recommended as a reliable procedure for the diagnosis of early pregnancy. Late in gestation the estrogen level becomes sufficiently high to make estrogen tests of more significance.

**Colostrum Test for Pregnancy**—Falls and his associates<sup>17</sup> noted that pregnant women failed to develop a local reaction around the site of an intracutaneous injection of colostrum in contrast to a wheal found in non-pregnant patients. They advocated the procedure as a test for pregnancy. It has not been found by most workers to be sufficiently accurate to constitute a satisfactory diagnostic test.

## BIBLIOGRAPHY

### *Rh Factors*

- 1 Landsteiner K. and Wiener A. S. An Agglutinable Factor in Human Blood Recognized by Immune Sera for Rhesus Blood. *Proc. Soc. Exper Biol & Med.*, 43 223 1940.
- 2 Levine, P. The Role of Isoimmunization in Transfusion Accidents in Pregnancy and in Erythroblastosis Fetalis. *Am J Obst. & Gynec.*, 42 165, 1941.
- 3 Landsteiner K. and Wiener, A. S. Studies on Agglutination (Rh) in Human Blood Reacting with Anti Rhesus Sera and with Human Isoantibodies. *J Exper Med.*, 74 309 1941.
- 4 Wiener A. S. Distribution and Heredity of Variants of the Rh Type. *Science*, 98 182, 1943.
- 5 Levine, P. On the Hr Factor and the Rh Genetic Theory. *Science*, 102 1 1945.
- 6 Wiener A. S., Sonn E. B. and Belkin, R. B. Heredity and Distribution of the Rh Blood Types. *Proc. Soc. Exper Biol & Med.*, 54 238, 1943.
- 7 Levine, P. The Pathogenesis of Erythroblastosis Fetalis. *J. Pediat.*, 23 656 1943.
- 8 Wiener A. S. New Test (Blocking Test) for Rh Sensitization. *Proc. Soc. Exper Biol & Med.*, 56 173 1944.

### *Vaginal Smears*

- 9 Papanicolaou G. N. A New Procedure for Staining Vaginal Smears. *Science*, 95 438 1942.
- 10 Shorr E. New Technic for Staining Vaginal Smears. *Science*, 94 545 1941.
- 11 Papanicolaou, G. N. The Diagnosis of Early Pregnancy by the Vaginal Smear Method. *Proc. Soc. Exper Biol. & Med.*, 22 436, 1925.
- 12 Papanicolaou, G. N. and Traut, H. F. Diagnosis of Uterine Cancer by the Vaginal Smear. New York. The Commonwealth Fund, 1943.
- 13 Meigs, J. F., Graham, R. M., Fremont-Smith G., Kapnick, I. and Rawson, R. W. The Value of the Vaginal Smear in the Diagnosis of Uterine Cancer. *Surg., Gynec. & Obst.*, 77 449 1943.

### *Pregnancy Tests*

- 14 Weisman, A. I. and Coates, C. W.. The South African Frog (*Xenopus Laevis*) in Pregnancy Diagnosis, New York, Clark & Fritts, 1944.



- 15 Zondek, B, Sulman, F and Black, R The Hyperemia Effect of Gonadotropins on the Ovary and Its Use in a Rapid Pregnancy Test. J.A.M.A., 128:939, 1945
- 16 Guterman, H S A Human Pregnancy Test Based Upon a Color Reaction of Pregnanediol in the Urine J Clin Endocrinol., 4:262, 1944
- 17 Falls, F H, Freda, V C and Cohen, H H Skin Test for Diagnosis of Pregnancy Am J Obst & Gynec., 41:431, 1941

# Index to Volumes 27, 28 and 29

(1943, 1944 and 1945)\*

## SYMPOSIA

### 1943

*January* (Chicago)  
*March* (Nationwide)  
*May* (New York)  
*July* (Mayo Clinic)  
*September* (Boston)  
*November* (Philadelphia)

OFFICE GYNECOLOGY  
NUTRITION  
INFECTIOUS AND TROPICAL DISEASES  
PHYSICAL THERAPY  
SPECIFIC METHODS OF TREATMENT  
MEDICAL EMERGENCIES ON THE HOME FRONT

### 1944

*January* (Chicago)  
*March* (Nationwide)  
*May* (New York)  
*July* (Mayo Clinic)  
*September* (Boston)  
*November* (Philadelphia)

CARDIOVASCULAR AND BLOOD DISEASES  
CHRONIC DISEASES  
PSYCHOSOMATIC MEDICINE  
CHEMOTHERAPY  
SPECIFIC METHODS OF TREATMENT  
RECENT ADVANCES IN MEDICINE

### 1945

*January* (Chicago)  
*March* (Nationwide)  
*May* (New York)  
*July* (Mayo Clinic)  
*September* (Boston)  
*November* (Philadelphia)

NEUROPSYCHIATRIC DISEASES  
NEW DEVELOPMENTS IN MEDICINE  
INTERNAL MEDICINE IN GENERAL PRACTICE  
MEDICAL EMERGENCIES  
SPECIFIC METHODS OF TREATMENT  
RECENT ADVANCES IN GYNECOLOGY AND OBSTETRICS

ABDOMINAL angina 1944 May 729, 738  
blood vessels, diseases, digestive symptoms resulting from, 1944 May 704  
conditions, acute, differential diagnosis, 1943 Nov., 1463  
examination in gynecology, 1945 Nov., 1346  
migraine, 1944 May, 733  
pain acute, diagnosis, 1943 Nov 1456  
Abortion, early progesterone in, 1945 Jan., 264  
emergency aspects, 1945 July 853, 856  
habitual and threatened hormone therapy 1945 Nov., 1405  
infected 1945 Nov., 1493  
infectious in domestic animals 1943 May 698  
septic, penicillin in 1944 July 835

Abortion septic, sulfonamides in, 1944 July, 827  
threatened 1943 Nov., 1601 1603  
with severe hemorrhage 1943 Nov., 1603  
Abruptio placentae 1943 Nov., 1607  
1945 July, 855 857  
Abscess, intracranial emergency treatment, 1945 July 895  
Ischlorectal, operation for prevention and management of complications, 1943 Jan., 221  
of lung emergency aspects 1945 July 841  
multiple, staphylococcal bacteremia complicating penicillin in 1944 Sept., 1035  
surgical indications and treatment, 1945 Sept. 1288

\* NOTE: The volume year is given in *italic type*.

- Accidents, susceptibility to, 1944 May, 653
- Achilles tendon, bursitis of, 1943 July, 1143  
inflamed, 1943 July, 1143
- Achlorhydria, acid therapy, 1945 March, 426
- dyspepsia due to, 1944 July, 893
- malnutrition due to, 1943 March, 572
- Acidosis in chronic diffuse glomerulonephritis, 1945 Sept, 1193
- Acne vulgaris, hormone therapy, 1945 Sept, 1111
- Acromegaly, 1944 March, 477
- Actinomycosis, 1945 March, 338
- esophagotracheobronchial fistula due to, 1944 July, 1005
- Adams-Stokes syndrome, 1945 Sept, 1157
- Addison's disease, 1944 March, 478, 1945 July, 1016
- desoxycorticosterone acetate in, 1945 March, 435
- hypoglycemic crises in, 1943 Nov, 1621
- uterine concentration tests, 1944 Sept, 1244
- Adenitis, cervical, acute, in children, sulfonamides in, 1944 July, 887
- Adenoid bleeding, control of, 1944 Sept, 1120
- bronchosinusitis in infants and children, 1944 Sept, 1091
- Adenoidectomy in adenoid bronchosinusitis, 1944 Sept, 1095
- indications for, 1944 Nov, 1332
- Adenoids, gonadal factors, 1944 Nov, 1330
- Adenoma of bronchus, hemoptysis in, 1945 July, 843
- of pituitary, 1944 March, 475
- parathyroid, 1945 March, 390, 393
- Adenylic acid in nutrition, 1943 March, 483
- Adjustments to impersonal side of living, 1944 May, 536
- Adrenal cortex, disturbances, 1945 July, 1016
- extract, 1944 Sept, 1262
- in Addison's disease, 1944 March, 479
- lands, diseases of, 1944 March, 478
- hypoglycemia crises in 1943 Nov, 1621
- infarction of, 1943 Nov, 1553
- physiology, 1944 Sept, 1237, 1238
- hormones, clinical uses, 1944 Sept, 1260
- medulla, disturbances, 1945 July, 1016
- African tick fever 1943 May, 734
- trypanosomiasis, 1943 Nov, 1491
- Agglutination tests in brucellosis, 1943 May, 710, 1945 March, 353
- Agglutination tests in Rocky Mountain spotted fever, 1943 May, 730
- in shigellosis, 1943 May, 694
- in typhus fever, 1943 May, 781
- Aging process, effects of local anoxia on, 1944 May, 712
- Amnium, 1943 July, 1150
- Air, confined, as vehicle of infection, 1944 Nov, 1293
- disinfection, continuous, methods, 1944 Nov, 1306
- infectiousness, respiratory disease and, 1944 Nov, 1300
- sanitation, current progress in, 1944 Nov, 1293
- Akinetic seizures, 1945 Sept, 1117, 1123
- Alarm reaction of Selye, asthma and, 1944 Sept, 1082, 1088
- Albumin as diuretic, 1944 Sept, 1181
- bovine, 1945 Sept, 1091
- human, 1945 March, 433, Sept, 1086
- Albuminocytologic dissociation in acute infectious radiculoneuritis, 1945 Jan, 1
- Albuminuria, chronic, 1943 Jan, 235
- Alcohol injections for facial pain, 1945 Jan, 77
- use of in peptic ulcer, 1944 March, 412
- Alcoholic neuritis, 1943 March, 424
- pellagra, 1943 March, 393
- Alcoholism, criminal responsibility and, 1945 Jan, 212
- nutritional deficiency in, 1943 March, 321
- Alimentary tract, functional disturbances, 1944 March, 418
- Alkali therapy, adjuvant, with sulfonamides, 1944 July, 878
- Alkalies in peptic ulcer, 1944 March, 410
- Allergic arthritis, 1943 Sept., 1331
- asthma, preoperative and postoperative care in, 1944 July, 992
- Allergy as cause of chronic diarrhea in infants, 1944 Sept, 1202
- treatment, recent advances, 1944 Nov, 1334
- Alloxan as factor in diabetes, 1944 Sept., 1054, 1945 March, 436
- Altrigenderism, 1944 May, 536
- Aluminum hydroxide in hypoparathyroidism, 1945 March, 435
- in peptic ulcer 1944 Sept, 1166
- powder in silicosis, 1945 March, 437
- Amnesia, hysterical, 1944 May, 691
- Amblyopia, hysterical, 1944 May, 691
- toxic, vitamin therapy, 1943 March, 559
- Amebiasis, postwar problem of, 1945 July, 906

- Amebic dysentery 1943 May, 687, 688  
 691, Nov., 1480, 1481, 1944 Nov  
 1499, 1507  
 Amenorrhea 1943 Jan., 36, 1944 Sept  
 1221 1945 Nov., 1377  
 hormone therapy, 1943 Sept., 1374  
 1944 Sept., 1225 1945 Jan., 258  
 260, 263, Nov., 1375 1400  
 psychiatric aspects 1945 Nov., 1520  
 roentgen treatment, 1945 Nov., 1382  
 American mucocutaneous leishmaniasis,  
 1943 Nov., 1493  
 trypanosomiasis, 1943 Nov., 1492  
 Amugen, 1945 March 433  
 intravenous use, 1943 March 313  
 oral use, 1943 March 309  
 Amino acids 1943 March 303  
 parenteral uses, 1945 March 433  
 Aminophylline in asthma in children  
 1945 July 867  
 in bronchial asthma 1944 March  
 343, 347 350 351 Sept., 1089  
 in bronchiolitis, acute in infants 1944  
 Sept., 1105  
 in coronary thrombosis, 1944 Jan 6  
 in left ventricular failure 1943 Jan  
 140  
 Ammonium chloride in congestive heart  
 failure, 1944 March 385  
 Amputation stump, ideal, 1943 July  
 1109  
 Amputations, after treatment, physical  
 therapy in, 1943 July 1109  
 hypothermia in 1943 July 1173  
 Amyotrophic lateral sclerosis, 1944  
 March 449  
 Analgesia for labor at home, 1945 Nov.,  
 1536  
 Analgesics in convalescence 1945 Sept.  
 1212  
 Anaphylactoid purpura, 1945 July 880  
 Andresen diet in hemorrhagic peptic ul  
 cer 1943 Nov., 1582  
 Androgen therapy See *Testosterone*  
 Anemia, aplastic, 1944 March 378  
 thrombocytopenic purpura in, 1944  
 Jan., 179  
 blood transfusions in 1944 March  
 380  
 chronic, treatment 1944 March 368  
 due to depression of bone marrow,  
 1944 March 377  
 hemolytic, 1944 March 378  
 acute acquired 1945 May 695  
 of newborn, Rh factor and 1944  
 Jan., 244 246  
 in carcinoma of colon 1945 July, 958  
 in chronic diffuse glomerulonephritis  
 1945 Sept., 1198  
 in sprue 1943 March 455  
 iron deficiency 1944 March 371  
 Lederer's 1945 May 702  
 Anemia, macrocytic, 1945 Jan., 246  
 nutritional, 1943 March, 467, 479  
 multiple deficiency 1944 March 377  
 nutritional 1944 March 376  
 of hypothyroidism, 1944 March, 376  
 of pregnancy 1944 March 377  
 pernicious, 1943 March 467 477  
 1944 Jan., 214 1945 Jan., 229  
 clinical types, 1945 Jan., 230  
 liver therapy 1944 Jan., 227, March  
 374 1945 Jan., 242  
 nervous symptoms treatment, 1944  
 March 446  
 posterolateral sclerosis in, manage-  
 ment 1945 Jan., 245  
 refractory, 1944 March 378  
 severe, electrocardiogram in 1945  
 May 608  
 sickle cell 1944 March 379  
 abdominal symptoms, 1943 Nov  
 1474  
 suspension of discarded erythrocytes in,  
 1945 March, 432  
 Anesthesia general, curare in 1945  
 March 423  
 glove or stocking 1944 May 687  
 hysteric, 1944 May 684, 687  
 local new agents 1945 March 419  
 spinal single dose and continuous for  
 labor and vaginal delivery, 1945  
 Nov., 1538  
 surgical electrocardiogram in 1945  
 May 614  
 Anesthetization of lumbar ganglia in  
 phlebitis 1943 July 990  
 Aneurysm aortic, 1943 Sept. 1289  
 dissecting 1944 Jan. 112 May 735  
 cardiovascular syphilitic, 1944 Jan.,  
 70  
 Angina, abdominal, 1944 May, 729, 738  
 of effort, 1944 Jan., 22  
 pectoris, 1943 Sept., 1286 Nov., 1531  
 1944 Jan. 16 21  
 anoxemia test 1945 May 616  
 decubitus 1944 Sept., 1136  
 differential diagnosis, 1945 March  
 513  
 prognosis, 1944 Nov., 1344  
 testosterone in 1945 March 425  
 Anginal pain 1944 Jan., 17  
 Angiocardiography 1944 Nov 1343  
 Angioneurosis, 1944 May 722  
 Angioneurotic edema 1944 May 733  
 739  
 Angiosclerosis 1944 May, 722  
 Angiotonin 1944 May 726  
 Anhydrohydroxyprogesterone 1944 Sept  
 1257  
 Aniline dyes in burns, 1943 Sept 1232  
 1239  
 Ankle clonus in pyramidal tract lesions  
 1945 Jan., 56

- Anorectal surgery, complications, prevention and management, 1943 Jan, 209
- Anorexia nervosa, 1944 July, 903  
nutritional deficiency in, 1943 March, 322
- Anoxemia test in angina pectoris, 1945 May, 616
- Anoxia, effects in cerebral arteriosclerosis and aging process, 1944 May, 712  
on emotional control, 1944 May, 704  
narcosis and, 1944 May, 713  
organ sensitivity to, 1944 May, 712
- Anthrax, penicillin in, 1945 July, 835
- Antibiotics in dermatology, 1945 Sept, 1107
- Antihormones, 1944 Sept, 1233
- Antimony in schistosomiasis, 1943 May, 859, 860
- Antiseptics, urinary See under *Urinary tract infections*
- Antuitrin-S in hypermenorrhea, 1944 Sept, 1224
- Anuria, emergency aspects, 1943 Nov, 1572  
in infants and children, 1945 July, 874  
obstructive, treatment, 1943 Nov, 1573
- Anxiety, 1945 Nov, 1512  
in nutritional deficiency, 1943 March, 435  
later fate of, 1945 May, 747  
neurosis, 1944 May, 672  
in combat crews, 1945 May, 731  
manifested by cardiovascular symptoms, 1944 Nov, 1509  
by gastrointestinal symptoms, 1944 Nov, 1541
- Aorta, abdominal, arteriosclerosis of, 1944 May, 727, 739  
dissecting aneurysm of, 1944 Jan, 112, May, 735  
thrombosis of, 1944 May, 733, 739  
aneurysm, 1943 Sept, 1289, 1944 Jan, 70, 112, May, 735  
electrocardiograms in, 1945 May, 605  
angusta, 1944 May, 721  
coarctation of, 1944 Jan, 102  
electrocardiogram in, 1945 May, 605, 606  
regurgitation, syphilitic, 1944 Jan, 73, 84
- Aortitis, syphilitic, 1943 Sept, 1289, 1944 Jan, 70  
aneurysm formation in, 1944 Jan, 71  
arsenotherapy, 1944 March, 305
- Aperiodomenorrhea, 1944 Sept, 1222  
hormone therapy, 1944 Sept, 1225
- Aphasia in hemiplegia, treatment, 1944 March, 451
- A.P.L., 1944 Sept, 1250  
in hypermenorrhea, 1944 Sept, 1224
- A.P.L. test, 1944 Sept, 1242  
therapeutic, 1944 Sept, 1247
- Aplastic anemia, 1944 March, 378  
thrombocytopenic purpura in, 1944 Jan, 179
- Apoplexy, treatment, 1944 March, 449
- Appendiceal dyspepsia, 1944 March, 421
- Appendicitis, acute, in children, 1945 July, 879  
chronic, simulating peptic ulcer, 1945 May, 629
- Arboflavinosis, 1943 March, 399, 495, 514
- Army Air Forces, rehabilitation in, 1945 May 715  
rheumatic fever in, convalescent care, 1945 May, 765
- dysenteries in, in tropics, 1944 Nov, 1497
- fatigue and exhaustion states in, 1945 May, 771
- feeding of, 1943 March, 581
- foot disorders in, 1943 July, 1129
- gastrointestinal neuroses in, 1944 Nov, 1541
- neurocirculatory asthenia in, 1944 Nov, 1509
- physical therapy in, symposium on, 1943 July, 1024
- primary atypical pneumonia in, in tropics, 1944 Nov, 1490
- reconditioning programs, 1945 May, 788
- skin diseases, in tropics, 1944 Nov, 1532
- thyroid disease in, in soldiers overseas, 1944 Nov., 1527
- Arrhythmia, cardiac, troublesome and crippling attacks, 1944 Sept, 1139
- Arrhythmias, 1945 Sept, 1154
- digitals in, 1945 March, 531
- quinidine in, 1945 Jan, 216
- Arsenic in chronic myeloid leukemia, 1944 Nov, 1384  
sensitivity and dermatitis, ascorbic acid in, 1943 March, 578
- Arsenicals, organic, thrombocytopenic purpura due to, 1944 Jan, 181
- Arsenotherapy, intensive, of early syphilis, 1944 March, 293  
of latent syphilis, 1944 March, 303  
of cardiovascular syphilis, 1944 March, 305  
of chronic myelocytic leukemia, 1944 Jan, 196  
of syphilis in pregnancy, 1945 Nov, 1466, 1467
- Arterial circulation, physical measures to improve, 1943 July, 962  
compression, intermittent, 1943 July, 989

- Arterial disease occlusive physical medicine in, 1943 July, 951  
in aged 1943 July, 1013  
physiologic mechanisms with therapeutic implications, 1943 Sept 1402  
occlusion, peripheral, 1943 Nov 1546  
Arteriolar-capillary fibrosis, 1944 May 723  
Arteriosclerosis, abdominal, 1944 May 719  
symptoms due to 1944 May, 726  
cerebral, effects of local anoxia on 1944 May, 712  
coronary, 1943 Sept., 1285  
etiology 1944 May 720  
obliterans, ischemic ulcers in tyrothricin for 1944 July, 851 855  
of abdominal aorta, 1944 May, 727 739  
pathology 1944 May 723  
renal, with hypertensive vascular disease, 1943 Jan., 237  
Arthralgias, 1943 Sept., 1311 1945 Sept. 1271  
Arthritic conditions common, treatment 1945 Sept., 1269  
Arthritis, 1943 Sept., 1320 1945 Sept., 1276  
allergic, 1943 Sept 1331  
backache due to 1943 July 1070  
gonorrheal, 1943 Sept., 1326  
in child, 1943 Jan., 80  
physical therapy in, 1943 July 915  
hypertrophic, 1943 Sept., 1338, 1945 Sept., 1278  
of hip physical therapy in, 1943 July 920  
of spine, physical therapy in, 1943 July 919  
physical therapy 1943 July, 1002  
hysterical, 1944 May 687 688  
infectious 1943 Sept., 1324  
sulfonamides in, 1943 Sept., 1327  
metabolic, 1943 Sept., 1318  
neuropathic 1943 Sept., 1331  
physical medicine in, 1945 May 790  
rheumatoid, 1943 Sept., 1332 1945 Sept., 1277  
advances in study and treatment, 1944 March 309  
etiology environmental factors, 1945 May 566  
fever therapy 1943 July 1123  
gold salts therapy 1943 Sept., 1336  
1944 March, 316 1945 Sept., 1277  
histamine and mecholyl fontophoresis in 1944 March 319  
neostigmine in 1945 March 423  
physiotherapy in, 1943 July 1008  
1944 March 313  
Arthritis rheumatoid vitamin D in, 1944 March 314  
Strümpell Marie 1943 Sept., 1338  
syphilitic 1943 Sept., 1326  
traumatic, 1943 Sept., 1322  
tuberculous 1943 Sept. 1326  
Arthroplasty physical therapy with 1943 July 916  
splint 1943 July 916  
Ascorbic acid assays, 1943 March 441  
deficiency 1943 March 441  
early 1943 March 495  
laboratory diagnosis 1943 March 502  
pathology 1943 March 515  
wound healing and 1943 March 561  
enzyme relationships 1943 March 283  
in arsenic sensitivity and dermatitis 1943 March 578  
in deficiency diseases, 1943 March 274  
in lead poisoning 1943 March 578  
in pregnancy 1943 March 540  
in wound healing, 1943 March 562 577  
requirements and sources, 1943 March 295, 442  
Aspiration biopsy of liver 1945 March 365  
Aspirin blood coagulation and, 1945 March 430  
Astasia-abasia hysterical, 1944 May 686  
Asthenia hypertension in 1944 May 721  
neurocirculatory 1944 May 569 666  
Sept., 1133  
due to small heart 1944 May, 577  
in soldiers overseas 1944 Nov., 1509  
Asthma, allergic, preoperative and post operative care in 1944 July, 992  
bronchial complications, unusual, 1945 March 456  
military service and 1945 March 455  
recent advances, 1945 March, 453  
treatment 1944 March, 339, 1945 March 458 461  
emergency aspects, 1945 July 843  
in children 1945 July 866  
pulmonary complications, postoperative treatment, 1944 July 995  
severe need for special treatment 1944 Sept., 1082  
with heart disease in children 1945 July 871  
Asthmatic bronchitis, preoperative and postoperative care in 1944 July 994  
patients undergoing surgical procedures, experience in care of 1944 July 991  
A T 10, 1944 Sept 1266  
in hypoparathyroidism 1943 Nov., 1627

- Atabrine in malaria, 1943 May, 627, Sept, 1423, Nov, 1480  
 Ataxia, hysteric, 1944 May, 686  
 Ataxic gait, tabetic, exercises for, 1944 March, 445  
 Atelectasis, massive, emergency aspects, 1945 July, 844  
 Atheroma, 1944 May, 723, 724  
 Athlete's foot, 1943 July, 1144, 1944 Nov, 1532  
 Atoxyl in African trypanosomiasis, 1943 May, 842  
 Atropine in coronary thrombosis, 1944 Jan, 3  
     in parkinsonism, 1944 March, 444  
 Audiometer tests of hearing, 1944 Nov, 1325, 1326  
 Auditory canal, external, furunculosis of, 1944 Sept, 1124  
 Aural granulations and polyps, 1944 March, 336  
 Auricular fibrillation, 1945 Sept., 1157  
     digitalis in, 1943 Jan, 145, 1945 March, 532  
     quinidine in, 1945 Jan, 217  
     flutter, 1945 Sept, 1156  
     digitalis in, 1945 March, 532  
     quinidine in, 1945 Jan, 223  
     tachycardia, paroxysmal, 1945 Sept, 1154  
 Aviation, ear problems in, 1944 Nov, 1320  
 Awakening, cataplexy of, 1944 July, 945  
 Axillary artery, aneurysm of, syphilitic, 1944 Jan, 80  
     nerve injuries, 1945 Jan, 23  
 Azotemia in kidney disease, treatment, 1944 Sept, 1183
- BABINSKI sign in pyramidal tract lesions, 1945 Jan, 47  
 Bacillary dysentery, 1943 May, 687, 692, Sept, 1206, 1213, Nov, 1481, 1944 Nov, 1498, 1507  
     postwar problem of, 1945 July, 905  
     sulfonamides in, 1944 July, 821, Nov, 1507  
 Bacillus coli meningitis, 1945 Sept, 1268  
 Back injuries and infections, physical therapy in, 1943 July, 919  
     strain, 1945 May, 568  
 Backache, differential diagnosis, 1943 July, 1062  
     in neurasthenia, 1944 May, 674  
     management, in military hospitals, 1943 July, 1057  
     manipulative therapy for, 1943 July, 1071  
     psychogenic, 1943 July, 1071  
 Bacteremia, puerperal, 1945 Nov, 1491  
     metastatic, 1945 Nov, 1492
- Bacteremia, staphylococcal, penicillin in, 1944 July, 860, Sept, 1031  
     sulfonamides in, 1944 July, 869  
 Balance, test for, 1944 July, 937  
 Bancroftian filariasis, 1943 May, 862, Nov, 1485  
 Bandages, elastic, in congestive heart failure, 1944 March, 386  
     use of, in after-treatment of amputations, 1943 July, 1115  
 Bandaging to prevent edema, 1943 July, 959  
 Bang's disease, 1943 May, 698, 702  
 Barbiturates in convalescence, 1945 Sept, 1213  
     in war psychoses, 1945 March, 418  
 Basal metabolic rate in endocrinology, 1944 Sept, 1244  
 Basophilism, pituitary, 1944 March, 477, 1945 July, 1011  
 Baths, contrast, in occlusive arterial disease, 1943 July, 963  
     in skin disease, 1945 Sept, 1096  
 Bayer 205 in African trypanosomiasis, 1943 May, 843  
 Bed rest in convalescence, undesirable effects, 1945 May, 720, 748, 809  
 Behavior Clinic of criminal court, 1945 Jan, 202  
 Behaviorism, 1944 March, 454  
 Belching, 1944 March, 419  
 Benzodrine in epilepsy, 1945 Sept, 1122  
     in prevention of motion sickness, 1945 March, 418  
     sulfate in seasickness, therapeutic evaluation in 100 cases, 1943 Nov, 1652  
 Beriberi, 1943 March, 409  
     diet in, 1945 May, 803  
     vitamin therapy, 1943 March, 274, 417  
 Bilharziasis, 1943 May, 848  
 Biliary calculi See Gallbladder disease  
     drainage by duodenal intubation, 1943 Nov, 1659  
     tract diseases, diagnosis, 1943 Nov, 1471  
 Bimanual examination in gonorrhea in women, 1943 Jan, 92  
 Biopsy, endometrial, 1943 Jan, 64, 1944 Sept, 1245, 1945 Jan, 252  
     in lymphogranuloma venereum, 1945 May, 678  
     liver, by aspiration, 1945 March, 365  
     testicular, 1944 Sept, 1246  
 Birth injuries, cerebral palsies due to, 1944 March, 448  
 Bismuth in early syphilis, supplementary to arsenicals, 1944 March, 299  
     in tonsillitis, 1944 Nov, 1332  
 Bladder atony, furmethide in, 1945 March, 421  
     decompression of, 1943 Nov, 1564

- Bladder female functional disturbances, management, 1945 Sept 1200  
neck obstruction, fibrous, 1945 Sept 1208  
neurogenic, 1943 Nov., 1566  
tabetic treatment, 1944 March 446  
Blastomycosis, 1945 March, 334  
Bleeding time Duke's method, 1944 Jan. 155  
Blepharitis ciliaris, 1943 March 556  
Blepharospasm, hysteric, 1944 May, 691  
Blindness, hysteric, 1944 May 691  
stimulated, 1944 July, 938  
Blood coagulation drugs influencing 1945 March 430  
count, white, peripheral, interpretation of 1944 July, 920  
derivatives indications and uses 1945 Sept 1069  
diseases, diagnosis and treatment, recent advances 1944 Jan., 148  
symposium on, 1944 Jan. 148  
donors, universal (Group O), 1945 Sept., 1077  
dyscrasias, ophthalmoscopic findings 1944 May, 750  
grouping technic, 1945 Sept., 1078  
groups, 1944 Jan., 233  
indications and uses, 1945 Sept., 1069  
laboratory findings in health and disease, 1945 Sept., 1314  
loss, acute, electrocardiogram in, 1945 May 613  
storage media for 1945 Sept., 1077  
substitutes, indications and uses, 1945 Sept., 1069, 1091  
use of 1943 Jan., 157, 161  
tests in endocrinology 1944 Sept., 1240  
transfusion. See *Transfusion*  
uses, physiologic background 1945 Sept. 1069  
vessels abdominal diseases of digestive symptoms referable to 1944 May 719  
peripheral effect of cigarette smoking on, 1945 July 949  
whole, use of, 1945 Sept., 1075  
Blood fluke disease 1943 May 848  
Blue nevus, 1944 July 973  
Blushing emotions and, 1944 May 572  
Body language, 1943 Nov., 1638  
Bone marrow cytology 1945 Sept., 1324  
depression of 1944 March 377  
examination in thrombocytopenic purpura, 1944 Jan., 158 167  
Bones, lesions, in hyperparathyroidism 1945 March 394 396  
Brachial birth palsy physical therapy in 1943 July 917  
plexus injuries 1945 Jan., 19  
physical therapy in, 1943 July, 917  
Bradycardia, emotions and 1944 May, 566  
Brain tumors, and optic neuritis, papilledema in, 1944 July, 957  
in children, 1945 July, 892  
vascular accidents 1943 Nov 1554  
Breakbone fever 1943 May, 808, 1944 Nov 1472  
Breast, aplasia and hypoplasia, 1945 Nov., 1395  
hypertrophy, 1945 Nov 1394  
pain in premenstrual, hormone therapy 1943 Sept., 1382  
Brewers yeast 1943 March, 300  
dosages, 1945 Sept., 1303  
in leukemia 1944 Nov., 1384  
Bright's disease See *Nephritis*  
Brill's disease, 1943 May, 786  
Bromides in convalescence 1945 Sept., 1214  
in epilepsy 1945 Sept., 1120  
Bromsalixol 1945 March 419  
Bromsulphalein test of liver function 1945 July 976  
Bronchial asthma See *Asthma*  
relaxation, repeated in obstructive dyspnea 1944 March, 339, 350  
Bronchiectasis, emergency aspects, 1945 July, 840  
surgical indications and treatment, 1945 Sept 1284  
Broncholititis of infants 1944 Sept., 1095  
Bronchitis, asthmatic, preoperative and postoperative care in 1944 July, 994  
chronic 1944 March 348  
Broncholithiasis, emergency aspects 1945 July 842  
Bronchopneumonia in infants and children 1945 July, 869  
penicillin in case report 1945 May 580  
Bronchosinusitis, adenoid in infants and children 1944 Sept., 1091  
Bronchus adenoma of, hemoptysis in, 1945 July 843  
Brucella, 1943 Jan., 266 May, 716, 1945 March 359  
Brucellosis, 1943 Jan., 259, May 698, 1945 March, 343  
diagnosis 1943 Jan., 262 May 704  
epidemiology, 1943 Jan., 259, May 700  
fever therapy in, 1943 July 920  
penicillin failure in 1945 May 586  
treatment and prevention 1943 Jan., 264 May 714 718  
Buboes inguinal in lymphogranuloma venereum 1945 May 668  
Bubonell 1945 May 669 670  
Buerger's disease. See *Thromboangiitis obliterans*  
exercises, 1943 July, 962



- Buerger-Allen exercises, 1943 July, 962  
 Bulgarian treatment of von Economo's encephalitis, 1943 May, 648  
 Bunion, 1943 July, 1141  
 Burns, aniline dyes in, 1943 Sept., 1232, 1239  
   blood and blood substitutes in, 1943 Jan., 170  
   complications, 1943 Sept., 1240, 1241  
   infection due to, penicillin in, 1945 July, 836  
   local treatment, 1943 Sept., 1231, 1236  
   plasma administration in, 1943 Sept., 1231, 1235  
   pressure dressing of Koch in, 1943 Sept., 1237  
   shock in, 1943 Sept., 1230, 1233  
     sodium lactate in, 1945 March, 438  
   skin grafting in, 1943 Sept., 1243  
   sulfonamides in, 1943 Sept., 1231, 1238  
   tannic acid in, 1943 Sept., 1232, 1237  
   toxemia of, 1943 Sept., 1236  
   treatment, 1943 Sept., 1229  
 Bursitis, foot, 1943 July, 1141  
   of Achilles tendon, 1943 July, 1143  
   subacromial, physical therapy in, 1943 July, 917  
   subdeltoid, diathermy in, 1943 July, 1184  
     physical therapy in, 1943 July, 917, 1012  
 Bush typhus, 1944 Nov., 1464
- CACHEXIA, pituitary, 1944 March, 474  
 Caffeine in epilepsy, 1945 Sept., 1122  
 Calciferol, 1944 Sept., 1265  
 Calcium as nutrient, 1943 March, 283  
   dietary requirements, 1943 March, 297  
   gluconate, colloidal, in sinusitis, 1944 Nov., 1329  
   in dermatology, 1945 Sept., 1104  
   low, neutral, diet, 1944 Sept., 1243  
   metabolism, physical therapy and, relationships, 1943 July, 1178  
   regulating compounds, 1944 Sept., 1263  
   therapy in pregnancy, 1943 March, 538  
 Calculi, biliary See *Gallbladder disease*  
 Calluses, 1943 July, 1135, 1142  
 Caloric requirements, 1943 March, 291  
 Candida albicans, infections with, 1945 March, 323  
 Capillary resistance test, Rumpel-Leede, 1944 Jan., 157  
 Carbarosone in amebic dysentery, 1943 May, 692, 1944 Nov., 1508  
 Carbohydrate metabolism, 1943 March 315  
   disorders of, 1943 March, 320  
   tolerance tests, 1944 Sept., 1241  
 Carbon dioxide in bronchial asthma, 1945 March, 459
- Carbuncles, penicillin in, 1945 July, 836  
 sulfonamides in, 1944 July, 845  
 Carcinoma of colon, proximal portion, iron deficiency and anemia associated with, 1945 July, 958  
   of esophagus, esophagotracheobronchial fistula in, 1944 July, 1002  
   of intestine, sulfasuxidine in, 1944 July, 823  
   of larynx, 1944 March, 323  
   of lung, emergency aspects, 1945 July, 842  
     primary surgical indications and treatment, 1945 Sept., 1282  
   of prostate, estrogen therapy, 1945 March, 435  
   of rectum, rectosigmoid and colon, errors in diagnosis, 1944 Jan., 278  
   of stomach, diagnosis, 1945 March, 489  
   dyspepsia in, 1944 July, 895, 897  
   gastroscopy in, 1945 March, 499  
   roentgen diagnosis, early, 1944 Nov., 1352  
   of uterus, diagnosis, vaginal smear for, 1945 Nov., 1551  
   of vulva, 1945 Nov., 1372  
 Cardiac See also *Heart*  
 Cardiophobia, 1944 May, 567  
 Cardiospasm, 1944 May, 589, 591  
   dyspepsia in, 1944 July, 891  
 Cardiovascular disease, hypertensive, 1943 Jan., 237, 238, 239  
   in aged, physical therapy in, 1943 July, 1013  
   ophthalmoscopic findings, 1944 May, 747  
   recent advances in, 1944 Nov., 1338  
   symposium on, 1944 Jan., 1  
   manifestations of anxiety neurosis, 1944 Nov., 1509  
   syphilis, arsenotherapy, 1944 March, 305  
   system, effect of emotions on, 1944 May, 565  
 Caries, dental, fluorine and, 1944 Nov., 1431  
   nutrition and, 1943 March, 547  
 Caruncle of urethra, 1945 July, 1007  
 Castellani's point, 1944 Nov., 1533  
 Cataplexy, 1944 March, 442  
   of awakening, 1944 July, 945  
   potassium chloride in, 1945 March, 422  
 Cataract, vitamin therapy, 1943 March, 559  
 Catarrh, gastric, with peptic ulcer, 1945 May, 628  
 Catheters, urethral, 1943 Nov., 1563, 1564  
 Cruda equina, injuries, 1943 July, 1086  
 Causalgia, 1945 Jan., 13  
 Cauterization of cervix in chronic cervicitis, 1945 July, 1002

- Cavernostomy in tuberculosis, 1945  
 March 450  
 Cavernous sinus thrombosis, emergency  
 treatment, 1945 July 894  
 Ceditanid, 1945 March, 424 529  
 in heart disease, 1944 Nov., 1345  
 Cellac disease, 1944 Sept., 1205  
 nutritional deficiency in, 1943 March  
 322  
 Cellulitis, pelvic, puerperal, 1945 Nov.,  
 1488  
 penicillin in, 1945 May, 584, July  
 836  
 Central artery of retina, occlusion of  
 1943 Nov., 1552  
 nervous system, manifestations of nu-  
 tritional deficiencies in, 1943 March  
 431  
 Cephalin-cholesterol flocculation test,  
 1944 Nov., 1358  
 Cerebral arteriosclerosis, effects of local  
 anoxia on 1944 May, 712  
 diplegia 1944 March, 448  
 embolism, 1943 Nov., 1554  
 hemorrhage 1943 Nov., 1554 1944  
 March, 449  
 palsies of children, treatment, 1944  
 March 448  
 rehabilitation in, 1945 May 792  
 819  
 thrombosis, 1943 Nov., 1554  
 in children, 1945 July, 894  
 Cerebrovascular accidents, 1943 Nov  
 1554  
 Cervical gland fluid examination in Afri-  
 can trypanosomiasis, 1943 May 839  
 Cervicitis, chronic, 1943 Jan 49 99  
 1945 July, 998  
 electrosurgical treatment, 1943 Jan,  
 52, 99  
 Cervix uteri diseases, as cause of leukor-  
 rhea, 1943 Jan 49  
 electrosurgery of, 1943 Jan., 6 53  
 103 105  
 erosions 1943 Jan., 6 53 100  
 smears from, 1943 Jan., 91  
 Cesarean section in eclampsia 1943 Nov.,  
 1600  
 Chagas' disease, 1943 May 822 Nov.,  
 1492  
 Chaddock's sign in pyramidal tract lesions,  
 1945 Jan., 50  
 Chancroid of vulva, 1945 Nov., 1368  
 sulfonamides in 1944 July 835 845  
 Charcot's joint, 1943 Sept., 1331  
 Chelosis in early nutritional deficiencies  
 1943 March 492  
 in riboflavin deficiency, 1943 March  
 399 400 405 550  
 Chemical balance hormones in maintain-  
 ing 1943 Nov 1615  
 tests for pregnancy 1945 Nov., 1554  
 Chemotherapy in bacteremia, 1944 July  
 869  
 in brucellosis, 1945 March, 357  
 in dermatology 1944 July 844  
 in infectious arthritides, 1943 Sept  
 1327  
 in intestinal diseases, 1944 July, 811  
 in lymphogranuloma venereum, 1945  
 May 682  
 in mastoiditis 1944 July, 799  
 in meningococcal infections, 1943 Sept.,  
 1204 1205, 1253, Nov., 1500 1944  
 July 869  
 in obstetrics and gynecology, 1944  
 July 827  
 in ophthalmology 1944 July, 789  
 in otolaryngology 1944 July, 789  
 in pediatrics, 1944 July 882  
 in pneumonia, 1943 Sept., 1299, Nov.,  
 1452 1944 July 805, Sept., 1068  
 in streptococcal infections, 1943 Sept.,  
 1203 1253  
 in tuberculosis, 1945 March, 445, July  
 918  
 in urinary tract infections 1943 Sept.,  
 1254 Nov., 1457 1944 July, 825,  
 1945 May 574, 575  
 Intraperitoneal in gynecology 1944  
 July, 833  
 parenteral use, in children, 1944 July,  
 883  
 present status, 1943 Sept. 1247  
 symposium on 1944 July 789  
 Chickenpox 1943 Nov., 1528  
 Chigoe flea bites, 1943 July, 1150  
 Childbirth See Labor  
 Children cardiac emergencies in, 1945  
 July 871  
 diseases, sulfonamides in 1944 July  
 882  
 feeding of 1943 Sept., 1355  
 gastrointestinal emergencies in 1945  
 July 878  
 neurologic emergencies in, 1945 July  
 886  
 refusal of food by management, 1943  
 Sept., 1369  
 respiratory tract emergencies in 1945  
 July, 864  
 urinary tract emergencies in 1945 July  
 874  
 Chinolone in amebic dysentery, 1943  
 May, 691 1944 Nov 1508  
 Chloral hydrate in convalescence, 1945  
 Sept. 1214  
 Cholecystitis, 1943 Nov., 1583 See also  
 Gallbladder disease  
 Cholera, 1943 May 766 Nov., 1490  
 postwar problem of 1945 July 901  
 treatment and prevention, 1943 May,  
 769 773 Nov., 1490  
 Cholesteatoma, 1944 March 335

- Cholesterothorax, 1945 March, 507, 510  
 Choline in cirrhosis of liver, 1945 March, 429, 484  
 Chordotomy for intractable pain, 1945 Jan, 98  
 Choreia, physical therapy in, 1943 July, 915  
 Choriomeningitis, lymphocytic, 1943 Nov, 1517  
     benign, 1945 Jan., 36  
 Chorionic gonadotropins, 1943 Jan, 10, 28, 31, 1944 Sept, 1250  
     hormone in hypermenorrhea, 1944 Sept, 1224  
 Chorioretinitis, 1943 March, 557  
 Chromoblastomycosis, 1945 March, 336  
 Chronic diseases, mental hygiene of, 1944 March 434  
     psychosomatic study in, 1943 Nov, 1636  
     symposium on, 1944 March, 291  
 Chylothorax, 1945 March, 506, 510  
 Cigarette smoking, effect on heart and peripheral blood vessels, 1945 July, 949  
 Circulatory system, disorders, psychosomatic factors in, 1944 May, 565  
 Circus movement, 1945 Jan, 216  
 Cirrhosis of liver, correlation of composite liver function study with liver biopsy, 1945 March, 363  
     diagnosis, 1945 March, 480  
     dietary treatment, 1945 March, 276, 429, 484, 485, May, 655  
     etiology, 1945 March, 273, 479  
     lipotropic substances in, 1945 March, 428, 484, May, 658  
     nutritional deficiencies as basis, 1945 May, 655  
     symptoms and signs, 1945 March, 275  
     treatment, recent advances, 1945 March, 273, 479  
     with clinical features of xanthomatous biliary cirrhosis but with confirmation at biopsy, 1945 July, 1054  
 Clavus hystericus, 1944 May, 687  
 Clawed hand in ulnar nerve injury, 1945 Jan, 15  
 Clay-shoveler's fracture, 1943 July, 1080  
 Climacteric See also *Menopause*  
     male, 1944 March, 483  
 Clitoris, hypertrophy, 1945 Nov, 1389  
 Clonus in pyramidal tract lesions, 1945 Jan, 56  
 Clorarsen in early syphilis, 1944 March, 299  
 Clot retraction test, 1944 Jan, 156  
 Coagulation time, Howell's method, 1944 Jan, 155  
 Coarctation of aorta, 1944 Jan., 102  
 Cobalt as nutrient, 1943 March, 285  
 Coccidioidal granuloma, 1943 May, 794, 798  
 Coccidioides immitis, 1943 May, 790  
 Coccidioidin, 1945 March, 334  
     serological tests, 1943 May, 802  
     skin test, 1943 May, 800  
 Coccidioidomycosis, 1943 May, 790, 1945 March, 332  
     postwar problem of, 1945 July, 907  
 Coccygodynia, physical therapy in, 1943 July, 920  
 Cod liver oil, 1943 March, 354  
     in rickets, 1943 March, 366  
 Coenzymes, 1943 March, 279  
 Coffee, permissibility, in peptic ulcer, 1944 Nov, 1351  
 Cold, application of, in military practice, 1943 July, 1166  
     common, glycol vapors for control, 1944 Nov, 1328  
     in armed forces in S Pacific, 1944 Nov, 1420  
     in infants and children, 1943 Nov, 1525  
     complications, sulfonamides in, 1944 July, 889  
     emotional factors in, 1944 May, 603  
     patulin in, 1944 Nov, 1328  
     propadrine hydrochloride in, 1945 March, 420  
     treatment, 1944 Sept, 1111  
 Colic, diagnostic import, 1943 Nov, 1464  
     in infants, 1943 Nov, 1524, 1945 July, 878  
     renal, 1943 Nov, 1569  
 Colitis, chronic ulcerative, sulfathalidine in, 1945 March, 427  
     functional, 1944 March, 418  
     mucous, 1944 March, 418  
     spastic, 1944 March, 418  
     ulcerative, due to lymphogranuloma venerea, sulfonamides in, 1944 July, 815  
     nonspecific, as a psychosomatic disease, 1944 May, 593  
     regional, sulfonamides in, 1944 July, 816  
     streptococcal, sulfonamides in, 1944 July, 811  
     sulfonamides in, 1943 Jan, 190, 193  
 Colon, carcinoma, errors in diagnosis, 1944 Jan, 278  
     diverticulitis and diverticulosis, clinical study, 1945 May, 639  
     infectious diseases, sulfonamides in, 1943 Jan, 189  
     irritable, 1943 Sept, 1385, 1944 March, 418  
     significance in management of cardiac disease, 1944 Jan, 109

- Colon, proximal portion, carcinoma of  
 iron deficiency and anemia associated  
 with 1945 July, 958  
 Colostomy test for pregnancy, 1945 Nov.,  
 1555  
 Coma, diabetic, 1945 July, 893  
 hysterical, 1944 May 690  
 in children, emergency treatment 1945  
 July 892  
 Comma bacillus, 1943 May 766  
 Communicable diseases common active  
 immunization against, 1945 Sept.,  
 1238  
 of infants, 1943 Nov., 1530  
 sulfonamides in, 1944 July 888  
 Complement fixation test in American  
 trypanosomiasis, 1943 May, 829  
 in typhus fever, 1943 May, 781  
 in lymphogranuloma venereum  
 1945 May 678  
 Compression sponge in prevention of ed-  
 ema, 1943 July 961  
 Compulsive-obsessive personality, 1944  
 May 545  
 Condylomata acuminata 1945 Nov., 1366  
 Congenital malformations as cause of  
 chronic diarrhea in infants, 1944 Sept.,  
 1195  
 Conization of cervix 1943 Jan., 53 105  
 Conjunctivitis, diet as cause 1943 March  
 556  
 gonorrheal sulfonamides in 1944 July  
 793, 886  
 in pellagra 1943 March 389  
 inclusion, sulfonamides in, 1944 July  
 793  
 lymphogranuloma venereum sulfona-  
 mides in, 1944 July 794  
 shipyard 1943 Nov., 1641  
 Constipation in functional disorders of  
 digestive tract, 1944 March, 420  
 in infants and children 1943 Nov.,  
 1524  
 Contractures, hysterical, 1944 May 685  
 686 698  
 Contrast baths in occlusive arterial dis-  
 ease, 1943 July 963  
 Convalescence bed rest in, undesirable ef-  
 fects, 1945 May 720 748, 809  
 in home rehabilitation problems 1945  
 May 818  
 in hospital rehabilitation problems,  
 1945 May 808  
 management of patient 1945 Sept.,  
 1210  
 Convalescent care of rheumatic fever in  
 Army Air Forces, 1945 May 765  
 hospital Army Air Forces role of 1945  
 May, 721  
 serum, 1945 Aug., 1085  
 types, doses and indications 1943  
 Jan., 157 158  
 Convalescent training program Army Air  
 Forces, 1945 May 716  
 ward need for 1945 May 812  
 Conversion hysteria 1944 May 532  
 Convulsions hysterical, 1944 May 690 698  
 in children emergency treatment 1945  
 July 886  
 in infancy and childhood 1943 Nov.,  
 1530  
 simulated 1944 May 702 July 940  
 Convulsive disorders, treatment, 1944  
 March 440  
 shock therapy in psychoses 1945 Sept.,  
 1232  
 Copper as nutrient, 1943 March 284  
 Cor pulmonale, pregnancy and 1945  
 Nov., 1450  
 Cornea, ulcers, vitamin therapy 1943  
 March 558  
 Corns 1943 July 1142  
 plantar 1943 July 1135  
 treatment in diabetes, 1944 July 980  
 Coronary arteriosclerosis 1943 Sept.,  
 1285  
 artery disease, 1944 Nov., 1344  
 digitalis in 1944 July 905  
 in hypertension 1943 Sept., 1263  
 ostia, stenosis of in syphilitic aortitis,  
 1944 Jan., 73  
 thrombosis, 1943 Nov., 1531 1533  
 1944 Jan., 1 1945 March 405  
 Sept., 1160  
 electrocardiograms in 1945 May 598  
 pain of differential diagnosis, 1945  
 March 513  
 quinidine in 1945 Jan., 221  
 restriction of activity in, and extent  
 of myocardial infarction 1945  
 March, 405  
 Creams dermatologic, 1945 Sept., 1100  
 protective 1945 Sept., 1103  
 Cretinism 1944 March 467  
 Criminal responsibility epilepsy and  
 1945 Jan., 212  
 insanity and 1945 Jan., 195  
 mental retardation and 1945 Jan.,  
 208  
 Croup 1945 July 864  
 in infants 1943 Nov., 1526  
 Cryptococcosis, 1945 March 335  
 Cultures, material for obtaining in gonor-  
 rhea in female 1943 Jan., 90  
 Curare, new uses, 1945 March 423  
 test for myasthenia gravis 1945 Jan.,  
 129  
 Cushing's syndrome 1944 March 471  
 1945 July 1011 Sept., 1224  
 Cutaneous. See Skin  
 Cyanosis in congenital heart disease 1944  
 Jan., 100  
 Cycloid personality 1944 May  
 547

- Cyst, suprasellar, obesity with, 1945 Sept, 1222
- Cystic disease of lung, emergency aspects, 1945 July, 845
- Cystine in liver disease, 1945 March, 429
- Cystitis, acute, in female, 1945 Sept, 1202
- chronic interstitial, 1945 Sept, 1205
- gonorrheal, 1943 Jan, 88
- interstitial, clinical aspects and treatment, 1944 July, 1008
- silver nitrate in, 1944 July, 1013
- Cystotomy, suprapubic, 1943 Nov, 1565
- DARK adaptation, poor, 1943 March, 355, 554
- D-desoxyephedrine hydrochloride, 1945 March, 420
- Deafness, conductive, relation to lymphoid hyperplasia of endometrium, and x-ray therapy, 1945 Sept, 1251
- hearing tests and, 1944 Nov, 1324
- in aviators, 1944 Nov, 1320
- in childhood, irradiation for, 1944 March 337
- simulated, 1944 July, 939
- vitamin therapy, 1944 Nov, 1325
- Debaryomyces neoformans, 1944 July, 950
- Decompression of bladder, 1943 Nov, 1564
- Deficiency diseases, arthralgia due to, 1945 Sept, 1271
- early, recognition and treatment, 1943 March, 485
- laboratory diagnosis, 1943 March, 501
- pathology, 1943 March, 509
- rehabilitation problems, 1945 May, 794
- role of gastrointestinal tract in conditioning, 1943 March, 519
- Dehydration, diagnostic import, 1943 Nov, 1466
- Delirium, electroencephalographic changes in, 1944 May, 632
- physiologic and psychologic considerations, 1944 May, 629
- Delivery See *Labor*
- Dementia praecox, 1944 May, 533, 667, 1945 Jan, 148
- Demerol, 1945 March, 417
- in convalescence, 1945 Sept., 1212
- Dengue fever, 1943 May, 808, Nov, 1483, 1944 Nov, 1471
- postwar problem of, 1945 July, 900
- Dental caries, diet and, 1943 March, 547
- fluorine and, 1944 Nov, 1431
- Depression in combat crews, 1945 May 732
- in returned soldiers, 1945 May, 736
- Dermacentroxenus rickettsi, 1943 May, 723
- Dermatitis, acute, emergency aspects, 1945 July, 833
- herpetiformis, sulfonamides in, 1944 July, 846
- pellagrous, 1943 March, 382
- venenata in soldiers in tropics, 1944 Nov, 1535
- Dermatology, nonsurgical emergencies encountered in, 1945 July, 833
- sulfonamides in, indications and limitations, 1944 July, 844
- Dermatomycosis pedum, 1943 July, 1144
- Dermatophytosis, 1945 March, 323
- treatment, 1945 March, 326
- Dermatoses, common, treatment, 1945 Sept, 1095
- Dermoid tumor of ovary, pregnancy complicating, in young girl, 1943 Jan, 23
- Desoxycorticosterone acetate, 1944 Sept, 1261
- in Addison's disease, 1944 March, 479, 1945 March, 435
- Desoxyephedronium sulfathiazole in sinusitis, 1944 Nov, 1328
- Diabetes insipidus, 1944 March, 478, 1945 July, 1009
- urine concentration tests, 1944 Sept, 1244
- melitus, 1945 July, 1014
- alloxan and, 1944 Sept, 1054
- causes of death in, 1944 Sept, 1061
- diet in, 1944 Sept, 1059
- etiology, 1943 March, 323
- insulin in, 1944 Sept, 1060, 1945 March, 436
- pregnancy in, 1945 Nov, 1477
- protamine-zinc insulin in, 1944 Sept, 1060
- Selective Service studies, 1944 Sept, 1055
- treatment, 1944 Sept, 1054
- tuberculosis and, association of, 1944 March, 493
- Diabetic coma, 1945 July, 893
- electrocardiogram in, 1945 May, 608
- gangrene, preinsulin and insulin cras, comparison, 1944 July, 978
- treatment, 1944 July, 981
- retinitis, 1944 May, 749
- Diammodiphenylsulfone in pneumonia, 1944 July, 810
- Diaphragmatic hernia, dyspepsia in 1944 July, 892
- Diarrhea, acute, in infants and children, 1945 July, 882
- chronic, in infants and children, 1944 Sept, 1189
- deficiency state due to, 1943 March, 524, 571

- Diarrhea, in functional disorders of digestive tract, 1944 March, 420  
 in sprue, 1943 March, 454  
 psychic factors in, 1944 May, 597  
 Diasona in tuberculosis, 1945 March 447 448 July, 921  
 Diathermy, calcium metabolism and 1943 July 1183  
 in occlusive arterial disease, 1943 July 967  
 Dichlorophenarsine hydrochloride in syphilis, 1945 March, 438  
 Dick test in scarlet fever, 1943 May, 666  
 toxin in scarlet fever, 1943 May, 668  
 Dicoumarol in prevention of embolism and thrombosis, 1945 March, 430, 431 July 840 929  
 Diencephalic syndrome, hypertension with 1943 Sept., 1261  
 Dienoestrol, 1945 March, 435  
 Diet in acidosis of chronic diffuse glomerulonephritis, 1945 Sept., 1196  
 Andresen, 1943 Nov., 1582  
 Army 1943 March, 581  
 basic, for sick patients, 1943 March 576  
 eye lesions and, 1943 March, 553  
 for infants, 1943 Sept., 1361  
 for older children 1943 Sept., 1361  
 for sick child 1943 Sept., 1366  
 in celiac disease, 1944 Sept., 1206  
 in cirrhosis of liver 1945 March, 276 427, 484 May 655  
 in convalescence, 1945 Sept. 1215  
 in deficiency diseases, 1943 March, 531  
 in diabetes mellitus, 1944 Sept., 1059  
 in epilepsy, 1945 Sept., 1119  
 in functional disorders of digestive tract 1944 March 423  
 in irritable stomach and colon 1943 Sept., 1388 1390 1394  
 in kidney disease, 1944 Sept., 1178  
 in nephrosis, 1945 Sept., 1186  
 in nutritional deficiencies, 1945 May 799-802  
 in obesity in children 1945 Sept., 1227  
 in peptic ulcer 1944 March 407 Nov 1531  
 fundamental importance in Army hospital 1945 May 706  
 in pernicious anemia 1945 Jan., 244  
 in pregnancy, 1943 March 537, 574  
 in recurrent peptic ulcer 1945 Sept., 1167  
 in rehabilitation, 1945 May 794  
 in renal disease, 1943 Jan., 243  
 in rheumatoid arthritis 1944 March 112  
 in sprue, 1943 March 462 463  
 inadequate malnutrition due to 1943 March 521 575  
 Mculengracht 1943 Nov., 1582  
 Diet, neutral low calcium, 1944 Sept., 1243  
 reduction, 1943 March 345, 346  
 requirements of, 1943 March, 288 299  
 Sippy, modified, 1943 Nov., 1581  
 teeth and, 1943 March 545  
 therapeutic, malnutrition due to 1943 March 522, 575  
 weight building for children, 1943 Sept., 1368  
 Diethylstilbestrol. See *Stilbestrol*  
 Digestive system functional disturbances 1944 March 418  
 symptoms referable to resulting from diseases of abdominal blood vessels 1944 May 719  
 Digifoline, 1943 Jan., 153  
 Digilamid 1943 Jan., 153, 1945 March 423  
 Digitaline natielle, 1945 March, 423  
 Digitalis, blood-clotting and 1945 March 431  
 dosage and administration 1943 Jan 152  
 effects on electrocardiogram 1945 May 609  
 in arrhythmias, 1945 March, 531  
 in congestive heart failure, 1944 March 382  
 in coronary artery disease, 1944 July, 905  
 in heart failure, 1945 March 524  
 preparations and uses, 1945 March 423, 524  
 pure form, use of 1944 Nov., 1345  
 toxic effects, 1943 Jan., 149  
 uses and abuses, 1943 Jan., 143  
 Digitil quinid varus, 1943 July 1134  
 Digitoxin 1943 Jan., 153 1945 March 423  
 Digoxin 1945 March 424, 529  
 Dihydrotachysterol 1944 Sept., 1266  
 in hyperparathyroidism, 1945 March 402  
 in hypoparathyroidism, 1943 Nov., 1627 1944 March, 472  
 Dilantin sodium in bronchial asthma 1945 March 459  
 Dilaudid in convalescence 1945 Sept., 1212  
 Diiodoquin in amebiasis, 1943 May 691  
 Diphenylhydantoin sodium in convulsive disorders, 1944 March 441  
 Diphtheria, 1943 Nov., 1529  
 epidemiology 1943 May 651  
 immunization, 1943 May 655 650 1945 Sept., 1240  
 in armed forces in S Pacific, 1944 Nov., 1421  
 laryngeal, 1945 July, 866  
 Shick test, 1943 May 656, 659

- Diplegia, cerebral, 1944 March, 448  
 Disama dia tulu, 1943 May, 841  
 Discomfort, gastro-intestinal, of functional origin, 1944 March, 419  
 Dislocations, physical therapy in, 1943 July, 914  
 Diuresis in congestive heart failure, mer-salyl and theophylline orally for, 1944 July, 911  
 in nephrosis, 1945 Sept., 1187  
 Diuretics in congestive heart failure, 1944 March, 384  
 in kidney disease, 1944 Sept., 1180  
 mercurial, intravenous, toxic effects, 1944 Nov., 1346  
 new, 1945 March, 424  
 Diverticulitis of colon, 1945 May, 639  
 clinical study, 1945 May, 639  
 sulfonamides in, 1944 July, 823  
 Diverticulum, urethral, 1945 July, 1008  
 Drop wrist in radial nerve injury, 1945 Jan., 10  
 Drug reaction, serum transfusion in, 1943 Jan., 169  
 Ductus arteriosus, patent, 1944 Jan., 98, 102  
 congenital, evaluation of surgical treatment, 1944 March, 388  
 x-ray signs, 1944 Nov., 1352  
 Duodenal intubation, biliary drainage by, 1943 Nov., 1659  
 ulcer See also *Peptic ulcer*  
 differential diagnosis, 1943 Jan., 195  
 dyspepsia in, 1944 July, 897  
 Dust, house, allergy to, 1944 Nov., 1334  
 Dust-suppressive measures for reducing infectivity of air, 1944 Nov., 1312  
 Dwarfism, pituitary, 1944 March, 476  
 Dye excretion tests of liver function, 1945 July, 976  
 typing for differentiation of brucella, 1943 May, 600  
 Dysentery, 1943 May, 687, 1944 Nov., 1497  
 amebic, 1943 May, 687, 688, 691, Nov. 1480, 1481, 1944 Nov., 1499, 1507  
 postwar problem of, 1945 July, 906  
 bacillary, 1943 May, 687, 692, Sept. 1206, 1213, Nov., 1481, 1944 Nov., 1498, 1507  
 postwar problem of, 1945 July, 905  
 sulfasuxidine in, 1945 March, 426  
 sulfathalidine in, 1945 March, 426  
 sulfonamides in, 1943 May, 695, Sept., 1207, 1208, 1216, 1254, Nov., 1482, 1944 July, 821, Nov., 1507, 1945 Sept., 1311  
 in children, sulfonamides in, 1944 July, 888  
 Dysmenorrhea, 1943 Jan., 34, 1945 Nov., 1410  
 Dysmenorrhea, hormone therapy, 1943 Jan., 34, Sept., 1376, 1945 Jan., 259, 262, 265, 267, Nov., 1400, 1413  
 pessaries in, 1943, Jan., 114  
 psychiatric aspects, 1945 Nov., 1520  
 Dyspareunia, 1945 Nov., 1372  
 Dyspepsia, 1944 July, 891  
 appendiceal, 1944 March, 421  
 from extragastric systemic disease, 1944 July, 902  
 from organic disease or abnormalities of stomach, esophagus or duodenum, 1944 July, 891  
 functional, 1944 March, 418, July, 902  
 gallbladder, 1944 March, 421  
 in military personnel, 1944 Nov., 1353  
 reflex, 1944 July, 900  
 Dysphagia in syphilitic aortic aneurysm, 1944 Jan., 75  
 Dyspnea, obstructive, 1944 March, 339, 340  
 pulmonary disturbances causing, emergency aspects, 1945 July, 843  
 Dyspragia intermittens angiosclerotica intestinalis, 1944 May, 729, 738  
 Dyssebacia in early nutritional deficiencies, 1943 March, 490  
 in pellagra, 1943 March, 385  
 Dystrophia adiposogenitalis, 1944 March 474  
 EAGLE systems in early syphilis, 1944 March, 299  
 Ear, blast injuries, 1944 Nov., 1321  
 cholesteatoma, 1944 March, 335  
 diseases of, chronic, 1944 March, 330, 334  
 recent advances in, 1944 Nov., 1320  
 sulfonamides in, 1944 July, 797  
 local use, 1944 July, 800  
 treatment by general practitioner, 1944 Sept., 1108  
 granulations and polyps, 1944 March, 336  
 problems in aviators, 1944 Nov., 1320  
 Earache, 1944 Sept., 1124  
 Eardrum, perforations, 1944 March, 334  
 Ears, draining, treatment, 1944 Sept., 1125, 1126  
 itching, treatment, 1944 Sept., 1123  
 swimming in relation to, 1944 Sept., 1126  
 Eclampsia, 1943 Nov., 1596, 1599, 1945 July, 852, Nov. 1436, 1443  
 Ecthyma, sulfathiazole in, topically, 1944 July, 847  
 Ectopic pregnancy, 1943 Nov., 1601, 1603  
 ruptured, 1945 July, 854, 856  
 Edema, angioneurotic, 1944 May, 733, 739  
 in congestive heart failure, prevention and treatment, 1944 March, 384

- Edema, nephrotic, 1943 Jan., 245, 1944 Sept., 1181  
 nutritional, 1943 March 307  
 of lung, acute, emergency aspects 1945 July, 837  
 prevention, in peripheral vascular disease, 1943 July 958  
 pulmonary acute in congestive heart failure, 1944 March 386  
 Educational retraining in Army Air Forces, 1943 May, 721  
 Efficiency test of hearing 1944 Nov., 1321  
 Effluence in fibrositis, 1943 July, 906  
 Effort syndrome, 1944 May, 569  
 due to small heart, 1944 May 517  
 Ego structure, modification as cause of increase in gastro-intestinal disorders in World War II, 1944 May 561  
 El tabardillo 1943 May, 775  
 Electric convulsive therapy of mental disease, 1943 July, 1019  
 Electrocardiography in heart blocks, 1944 Jan., 56  
 in rheumatic heart disease, 1944 Jan., 130  
 recent advances, 1944 Nov., 1339  
 uses in medicine, 1945 May 590  
 ventricular gradient in, 1945 March 464  
 Electrocoagulation of cervix, 1943 Jan., 6, 53 103  
 Electrocoagulation of cervix, 1943 Jan., 103  
 Electrodiagnosis in peripheral nerve injuries, 1945 Jan., 23  
 Electromorphology in delirium, 1944 May 632  
 in epilepsy, 1945 Sept., 1118 1126  
 in stuttering, 1944 May 619  
 Electrophysiology of muscle, 1943 July 936  
 Electroshock therapy in psychoses 1945 Sept., 1232  
 with insomnia, 1945 Jan., 192  
 outpatient, in psychiatric disorders 1945 Jan., 165  
 Electrosurgery in chronic cervicitis, 1943 Jan., 6 53 99  
 Electrotherapy in neuroses, 1944 March 462 465  
 in peripheral nerve injuries 1943 July 1100  
 Elephantiasis, 1943 May 265  
 treatment, 1943 May 86  
 Elephantoid fever 1943 May 264  
 Embolism, 1943 Nov., 1545  
 arterial, 1943 Nov., 1545  
 cerebral, 1943 Nov., 1544  
 mesenteric, 1943 Nov., 1552  
 prevention, dicoumarol in, 1945 March 430 431 July 840 929  
 heparin in, 1945 March 431 July 933  
 Embolism pulmonary, 1943 Nov 1550  
 emergency aspects 1945 July, 839  
 prevention exercises for, 1945 May 789  
 Emergencies medical on home front symposium on 1943 Nov., 1447  
 symposium on 1945 July 833  
 Emetine in amebic dysentery, 1943 May 691 1944 Nov 1507 1508  
 in schistosomiasis 1943 May, 860  
 Emotional control impairment, produced both by lowering and raising oxygen pressure in atmosphere, 1944 May, 704  
 problems, 1943 Nov., 1634  
 states arthralgia due to, 1945 Sept 1271  
 Emotions as factor in some young children's colds, 1944 May, 603  
 in ulcerative colitis, 1944 May, 594  
 disturbances of gastro intestinal disorders due to 1944 Sept., 1154  
 effect on cardiovascular system, 1944 May, 565  
 neurophysiology of 1945 May, 744  
 relationship to physiologic processes, 1944 May 556  
 role in hysterical symptoms, 1944 May, 555  
 tangibility of 1944 May, 546  
 Emphysema pulmonary, obstructive, 1944 March, 356  
 Emprosthotonos, hysterical, 1944 May 690  
 Empyema, pyogenic, 1945 March, 507, 510  
 Emulsions, 1945 Sept., 1099  
 Encephalitis 1943 Nov., 1497, 1506  
 epidemic, of North America 1943 May 632  
 Encephalitis, 1943 Nov., 1506  
 acute emergency treatment, 1945 July, 895  
 eastern equine type 1943 Nov., 1511  
 epidemic, 1943 May 632, Nov., 1501  
 arthropod borne virus types, 1943 May, 633  
 serological tests, 1943 May 642  
 vaccines in prevention, 1943 May, 645  
 neurological residuals 1943 Nov., 1507  
 St Louis type 1943 May, 633 Nov., 1507  
 summer type 1943 Nov., 1509  
 von Economo's type 1943 May 645 Nov., 1507  
 western equine type 1943 May 633 Nov., 1512  
 hemorrhagic, postinfection 1943 Nov 1517  
 Japanese, 1943 Nov., 1513



- Encephalitis lethargica, 1943 May, 632, Nov, 1507  
 Russian, 1943 Nov, 1513
- Encephalo-myelo-radikuloneuritis, acute, 1945 Jan, 1
- Endamoeba histolytica, 1943 May, 688
- Endarteritis obliterans, physical medicine in, 1943 July, 951
- Endocarditis, bacterial, subacute, 1944 Jan, 86, Sept, 1132  
 nonhemolytic streptococcus, treatment with penicillin, 1945 Sept, 1229  
 penicillin in, 1945 May, 583  
 therapeutics, 1945 March, 425  
 brucella, 1945 March, 348
- Endocervicitis, dysmenorrhea due to, 1945 Nov, 1411
- Endocrine diagnostic procedures, 1944 Sept., 1240  
 disturbances, acute, 1943 Nov, 1614  
 chronic, 1944 March, 467  
 hypertension in, 1943 Sept, 1262  
 hypoglycemic crises in, 1943 Nov, 1617  
 factors in abnormal and subnormal genital development, 1945 Nov, 1387  
 glands, real versus supposed disturbances, 1945 July, 1009  
 problems in gynecological practice, 1943 Jan, 9, 27  
 system, therapeutics, 1945 March, 433  
 therapy in dermatology, 1945 Sept, 1111  
 in frontal headaches in girls and women, 1944 Nov, 1329  
 in gynecological disorders, 1943 Jan, 27, Sept., 1373, 1944 Sept, 1223  
 in menopausal arthralgia, 1943 Sept, 1316  
 in menopause, 1945 Nov, 1421  
 in menstrual disorders, 1944 Sept, 1223, 1945 Jan, 251, Nov, 1375, 1413, 1421  
 in peptic ulcer, 1944 Nov, 1349  
 uses and abuses, 1945 Nov, 1396
- Endocrinology, syndromes masquerading under, 1944 Sept, 1273  
 synopsis of normal and pathologic physiology, diagnostic procedures and therapy, 1944 Sept, 1232
- Endometrial biopsy, 1943 Jan, 64, 1944 Sept., 1245, 1945 Jan, 252
- Endometritis, puerperal, 1945 Nov, 1486, 1537
- Enemas, avoidance in functional disorders of digestive tract, 1944 March, 426
- Enfermedad de Chagas, 1943 May, 822
- Enteritis, regional, sulfonamides in, 1944 July, 819
- Enterogastrone in peptic ulcer, 1944 Nov, 1349
- Enuresis, ephedrine in, 1945 March, 420
- Enzymes, 1943 March, 279  
 vitamin relationships, 1943 March, 280
- Eosinophilia, clinical occurrence, 1944 July, 915
- Ephedrine in asthma in children, 1945 July, 867  
 in enuresis, 1945 March, 420  
 in myasthenia gravis, 1945 Jan, 134, March, 421  
 sulfate in pulmonary emphysema, 1944 March, 365
- Epidemic diseases in wartime, 1943 Sept., 1201
- Epidermatophytosis, 1945 March, 323  
 of feet, in soldiers in tropics, treatment, 1944 Nov, 1532
- Epidural hemorrhage, 1943 Nov, 1557
- Epilepsy, criminal responsibility and, 1945 Jan, 212  
 diagnosis, 1945 Sept, 1114  
 electrocardiogram in, 1945 May, 608  
 electroencephalography in, 1945 Sept, 1118, 1126  
 glutamic acid in, 1945 March, 418  
 treatment, 1945 Sept, 1114, 1119  
 types of seizures, 1945 Sept, 1115
- Epinephrine, 1944 Sept, 1263  
 in asthma in children, 1945 July, 867  
 in bronchial asthma, 1944 Sept, 1089  
 in bronchiolitis, acute, in infants, 1944 Sept, 1105  
 inhalation, in bronchial asthma, 1944 March, 346, 350
- Epistaxis, gonadal relationships, 1944 Nov, 1330  
 treatment, 1944 Sept, 1116
- Erb's paralysis in brachial plexus injuries, 1945 Jan, 19
- Erosions, cervical, 1943 Jan, 49, 100  
 electrosurgical treatment, 1943 Jan, 6, 53, 100
- Erysipelas, sulfonamides in, 1944 July, 845  
 penicillin in, 1945 July, 836
- Erysipeloid, penicillin in, 1945 July, 836
- Erythroblastosis foetalis, development of manifestations of, 1944 Jan, 244  
 pathogenesis, 1944 Jan, 245  
 Rh factor and, 1944 Jan, 240, 258  
 transfusion therapy, 1944 Jan, 251, 263
- Erythrocytes, resuspended, uses of, 1945 March, 432, Sept, 1077  
 sedimentation rate, clinical significance, 1945 July, 937
- Esophagotracheobronchial fistula, 1944 July, 1001
- Esophagus, tumor, dyspepsia in, 1944 July, 892  
 ulcer, dyspepsia in, 1944 July, 892
- Espundia, 1943 Nov, 1493



- Feeble-mindedness, criminal responsibility and, 1945 Jan, 208
- Feeding of infants and children, 1943 Sept, 1355, Nov, 1521  
of premature infants, 1943 Nov, 1520
- Feet See *Foot*
- Female sex hormone See *Estrogen*
- Femoral nerve injuries, 1945 Jan, 23
- Femur, osteomyelitis, chronic, penicillin in, 1944 Sept, 1038
- Ferrous carbonate in facial pain, 1945 Jan, 77
- Fetal erythroblastosis, Rh factor and, 1944 Jan, 240, 258
- Fever, artificially induced, leukocyte response to, 1944 July, 923, 925  
therapy in brucellosis, 1945 March, 360  
in brucellosis, 1943 Jan, 267, May, 717  
in cardiospasm, 1944 May, 592  
in early syphilis, combined with intensive arsenotherapy, 1944 March, 297  
in gonorrhea, 1944 March, 507  
in women, 1943 Jan, 96  
in rheumatoid arthritis, 1943 July, 1123
- Fibrin foam and film, 1945 Sept, 1087  
in neurosurgery, 1945 March, 432
- Fibrosis, arteriolar-capillary, 1944 May, 723
- Fibrositis, environmental factors, 1945 May, 568  
pancreatic, chronic diarrhea in infants due to, 1944 Sept, 1198  
with ecstasia, 1944 May, 724
- Fibrotic headache, 1943 July, 905
- Fibrositis, physical therapy in, 1943 July, 903, 919  
in aged, 1943 July, 1011
- Field's stain for malarial parasites, 1944 Nov, 1459
- Filariasis, bancroftian, 1943 May, 862, Nov, 1487  
postwar problem of, 1945 July, 903
- Fish liver oils, 1943 March, 354  
in rickets, 1943 March, 366
- Fissure in ano, operation for, prevention and management of complications, 1943 Jan, 219
- Fistula, esophagotracheobronchial, 1944 July, 1001  
gastrointestinal, deficiency state due to, 1943 March, 523, 572  
in ano, operation for, prevention and management of complications, 1943 Jan, 222
- Fits See *Convulsive disorders*
- Five-day drip in early syphilis, 1944 March, 293
- Fleckfeber, 1943 May, 775
- Fluids, administration, in chronic diffuse glomerulonephritis, 1945 Sept, 1193  
in diarrheas of infancy, 1945 July, 882
- Fluorescence test for dermatophytosis, 1945 March, 325
- Fluorine, beneficial and harmful effects on human teeth, 1944 Nov, 1428
- Focal fit, 1945 Sept, 1115, 1122
- Follicle-stimulating hormone, 1943 Jan, 27  
in menstrual disorders, 1944 Sept, 1225
- Folliculins, 1944 Sept, 1251
- Follutein in hypermenorrhea, 1944 Sept, 1224
- Food habits, and obesity, 1943 March, 339
- Foods, composition, 1943 March, 290  
nutritive values, 1943 March, 287, 588, 591  
losses in preparation, 1943 March, 585
- Foot, athlete's, in soldiers in tropics, treatment, 1944 Nov, 1532  
care of, in peripheral vascular disease, 1943 July, 956  
dermatophytosis of, 1945 March, 323  
disabilities, management in Army, 1943 July, 1129  
physical therapy in, 1943 July, 920  
exercises, 1943 Sept, 1314  
fractures, 1943 July, 1145  
gunshot wounds, 1943 July, 1147  
hygiene of, in diabetes, 1944 July, 979  
malalignment, posture and, 1943 July, 937  
painful, 1943 July, 1139  
puncture wounds, 1943 July, 1147  
ringworm of, 1944 Nov, 1532  
sprains, 1943 July, 1146  
tropical diseases, 1943 July, 1149  
vasomotor disturbances, 1943 July, 1148  
wounds, penetrating, 1943 July, 1145
- Foreign body in urethra, acute retention due to, 1943 Nov, 1566
- Formulas for infant feeding, 1943 Sept, 1356
- Fowler's solution in African trypanosomiasis, 1943 May, 842
- Fractures in hyperparathyroidism, 1945 March, 394  
nasal, treatment, 1944 Sept, 1121  
of foot, 1943 July, 1145  
of spine, arthritis in, 1943 Sept, 1332  
of spinous process, 1943 July, 1080  
of transverse processes, 1943 July, 1079  
of vertebral bodies, 1943 July, 1080  
physical therapy in, 1943 July, 913

- Fractures, physical therapy in to promote calcium metabolism 1943 July, 1183
- Frambesia 1943 Nov., 1495
- Frazer's solution, 1944 Nov., 1533
- Frei test, 1945 May 677
- inverted 1945 May 678
- Frenkel walking exercises, 1944 March 445
- Friedländer's bacillus pneumonia 1943 Sept., 1292
- Friedreich's disease, electrocardiogram in 1945 May 607
- Frigidity psychiatric aspects, 1945 Nov., 1521
- testosterone in, 1943 Sept., 1383
- Frog test for pregnancy 1945 Nov 1553
- Frohlich's syndrome, 1945 Sept., 1222
- Frost bite, hypothermia in, 1943 July 1173
- F S H test 1944 Sept., 1242
- Fuadin in schistosomiasis 1943 May, 859
- Functional tests, electrocardiogram in 1945 May 615
- Fungus infection of vulva 1945 Nov., 1365
- pleural effusions of 1945 March 508 511
- sodium propionate in, 1945 March 438
- Furmetide in bladder atony 1945 March 421
- Furuncle of external auditory canal, 1944 Sept 1124
- of nose with cellulitis of face, penicillin in 1944 Sept. 1037
- Furunculosis, penicillin in 1945 July 836
- Fusosporilliosis of vagina, 1945 Nov., 1361
- of vulva, 1945 Nov., 1370
- GALACTOSE tolerance test of liver function 1945 July 977
- Gallbladder disease, electrocardiograms in, 1945 May 606
- Gastric analysis, diagnostic value, 1945 March 492
- Gastritis 1944 Nov 1352
- as cause of dyspepsia, 1944 July, 894
- diagnosis 1945 March 489
- gastroscopy in 1945 March 498
- in military personnel 1944 Nov 1354
- Gastrointestinal disease diagnosis 1945 March 489
- Gastroenterology recent advances, 1944 Nov., 1349
- Gastrointestinal diseases psychosomatic manifestations 1944 Nov 1355
- disorders, early emotional outburst, as source of 1944 May 557 562
- functional 1944 March 418, Sept 1154
- in infants 1943 Nov., 1524
- Gastrointestinal disorders, increase in World War II 1944 May, 561
- emergencies, 1943 Nov., 1575
- hemorrhage, 1943 Nov., 1578
- neuroses 1944 Nov., 1541
- tract, abnormalities, significance in management of cardiac disorders 1944 Jan., 107
- acute nonsurgical emergencies related to 1945 July, 878
- anomalies as cause of chronic diarrhea in infants 1944 Sept., 1195
- role in conditioning deficiency diseases, 1943 March 519
- therapeutics 1945 March 426
- Gastroscopy 1943 March, 497
- Gehrung pessary 1943 Jan., 117 118, 119
- Gelatin as blood substitute 1945 March 433 Sept., 1091
- Gellhorn pessary 1943 Jan., 119
- Genital development, abnormal and subnormal endocrine factors in 1945 Nov., 1387
- Genito-urinary tract, disorders in infants, 1943 Nov., 1526
- Geriatrics, physical therapy in 1943 July, 1007
- Germicidal vapors, disinfection of air with 1944 Nov 1309
- Giemsa's stain for malarial parasites, 1944 Nov., 1459
- Gingivitis in infants, 1943 Nov., 1525
- nutrition and, 1943 March 548
- Girls, adolescent gynecological problems, 1943 Jan., 17
- Glandular physiology résumé 1944 Sept., 1233
- Globin insulin in diabetes 1945 March 436
- Globulin serum, immune, 1945 Sept., 1087
- Globus hystericus, 1944 May 689
- Glomerulonephritis 1943 Jan., 227, 229, 233
- acute in children electrocardiogram in 1945 May 606
- penicillin in, 1945 May 582
- treatment 1944 Sept., 1185
- chronic diffuse, management, 1945 Sept., 1184
- differential diagnosis, 1945 July 990
- Glomerulosclerosis intercapillary, 1945 March 538
- Glossitis in early nutritional deficiencies, 1943 March 490
- in nicotinic acid deficiency 1943 March 389
- in pellagra 1943 March 389
- in riboflavin deficiency 1943 M 402 405
- in sprue 1943 March 454

- Glucose in bronchial asthma, 1944 March, 345, 351  
tolerance test, 1944 Sept, 1241
- Glucose-insulin tolerance test, 1944 Sept, 1241
- Glucosides, cardiac, 1945 March, 423, 529
- Glutamic acid in epilepsy, 1945 March, 418, Sept, 1122
- Glycine in myasthenia gravis, 1945 Jan, 135
- Glycol vapors, disinfection of air with, 1944 Nov, 1310  
in control of common cold, 1944 Nov, 1328
- Goiter, exophthalmic, thiouracil in, 1944 Sept, 1043, Nov, 1362  
with severe exophthalmos, treatment, 1944 March, 484
- Gold salts in rheumatoid arthritis, 1943 Sept, 1336, 1944 March, 316  
therapy in arthritis, 1945 Sept, 1278  
thrombocytopenic purpura due to, 1944 Jan, 181
- Gonadal-nasopharyngeal relationships, 1944 Nov, 1329
- Gonadophysin, 1944 Sept, 1225
- Gonadotropin therapy in amenorrhea, 1945 Nov, 1380, 1400  
in dystrophia adiposogenitalis, 1944 March, 474  
in functional uterine bleeding, 1945 Nov, 1385, 1399  
in hypogonadism, 1944 March, 480, 481  
in menstrual disorders, 1945 Jan, 256  
in pituitary dwarfism, 1944 March, 476  
in sterility, 1945 Nov, 1403
- Gonadotropins, anterior pituitary, 1944 Sept, 1251  
chorionic, 1943 Jan, 10, 28, 31, 1944 Sept, 1250  
in menorrhagia, 1943 Jan, 38  
equine, 1943 Jan, 29
- Gonda sign in pyramidal tract lesions, 1945 Jan, 57
- Gonorrhea, fever therapy, 1944 March, 507  
in women, 1943 Jan, 5, 46, 83  
fever therapy, 1943 Jan, 96  
sulfonamide-resistant, penicillin in, 1944 July, 835  
sulfonamides in, 1943 Jan, 47, 93, 1944 July, 831  
local treatment, 1944 March, 509  
penicillin in, 1944 March, 507  
penicillin-resistant, 1945 May, 688  
sulfamerazine in, 1943 Nov, 1456  
sulfathiazole in, 1944 March, 506
- Gonorrhea, sulfathiazole in, asymptomatic carrier states following, 1944 March, 508
- sulfonamides in, 1943 Sept, 1254, 1945 Sept, 1311  
treatment under existing conditions, 1944 March, 506
- Gonorrheal arthritis, 1943 Sept, 1326  
in child, 1943 Jan, 80  
conjunctivitis, sulfonamides in, 1944 July, 793, 886  
cystitis, 1943 Jan, 88  
ophthalmia in child, 1943 Jan, 80  
vaginitis, 1943 Jan, 5, 46  
vulvovaginitis, 1943 Jan, 67, 1945 Nov, 1362  
sulfonamides in, 1944 July, 834
- Gordon's sign in pyramidal tract lesions, 1945 Jan, 53
- Gout, 1943 Sept, 1328  
etiology, environmental factors, 1945 May, 567
- Goute épaissie, 1943 May, 838
- Grafts, nerve, 1945 Jan, 27
- Gramicidin in dermatology, 1945 Sept, 1107
- Grand mal, 1945 Sept, 1116, 1122
- Granulations, aural, 1944 March, 336
- Granuloma, coccidioidal, 1943 May, 794, 798  
inguinale, 1945 Nov, 1369  
pyogenicum, 1944 July, 974
- Graves' disease with severe exophthalmos, treatment, 1944 March, 484
- Grippe in armed forces in S Pacific, 1944 Nov, 1420
- Groin, dermatophytosis of, 1945 March, 323
- Guanidine, in myasthenia gravis, 1945 Jan, 134
- Guillain-Barré syndrome, 1945 Jan, 1
- Gynecogens, 1944 Sept, 1251
- Gynecologic examination, 1943 Jan, 1, 1945 Nov, 1344  
problems of adolescent girl, 1943 Jan 17
- Gynecology, chemotherapy in, 1944 July, 827  
endocrine problems, 1943 Jan, 9, 27  
therapy, 1943 Jan, 27, Sept, 1373, 1944 Sept, 1217, 1232  
laboratory procedures in, 1945 Nov., 1546  
office, common problems, 1943 Jan 1  
symposium on, 1943 Jan, 1  
psychiatric aspects, 1945 Nov, 1508  
1519  
symposium on, 1945 Nov, 1343
- Gynecomastia, virginal, 1945 Nov, 1392
- HABITUS stiller, 1944 May, 721
- Haffkine's vaccine in plague prophylaxis, 1943 May, 763

Hair development, sexual, precocious  
 1945 Nov., 1390  
 dyes, organic, thrombocytopenic pur-  
 pura due to 1944 Jan., 182  
 Halibut Liver oil 1943 March 354  
 Hallux flexus, 1943 July, 1134  
 rigidus, 1943 July, 1134  
 valgus, 1943 July 1133  
 Hammer toe 1943 July, 1134  
 Hand, injuries and infections physical  
 therapy in, 1943 July 918  
 Head cold, treatment, 1944 Sept., 1111  
 injuries in children coma due to, 1945  
 July 893  
 emergency treatment 1945 July  
 891  
 Headache, fibrositic, 1943 July 905  
 frontal in girls and women, hormone  
 therapy 1944 Nov., 1329  
 in hypertension 1943 Sept., 1266  
 in neurasthenia, 1944 May, 674  
 menstrual, hormone therapy 1943  
 Sept., 1381 1944 Nov 1329  
 migrainous 1944 March 439  
 tension, 1944 March, 439 1945 May  
 568  
 treatment 1944 March 439  
 Hearing defects, simulated 1944 July  
 939  
 hysteric affections, 1944 May 692  
 neurasthenic affections, 1944 May 676  
 tests, 1944 Nov., 1324  
 new for selection of aviators, 1944  
 Nov., 1321  
 Heart block 1943 Nov 1540 1944  
 Jan 56  
 disease asthma with, in children, 1945  
 July 871  
 chronic, care of patient with 1944  
 March 381  
 common forms, treatment, 1943  
 Sept., 1279  
 congenital, common forms, 1944  
 Jan., 95  
 electrocardiograms in 1945 May  
 595  
 hypertensive, 1943 Sept., 1263 1288  
 with left ventricular enlargement  
 insomnia due to 1944 Sept.  
 1138  
 with left ventricular failure 1943  
 Jan., 125  
 management gastro-intestinal abnor-  
 malities as related to, 1944 Jan  
 107  
 neurotic symptoms in 1944 May  
 571  
 pain of differential diagnosis 1945  
 March 513  
 pregnancy and, management 1945  
 Nov., 1449  
 quinidine in 1945 Jan., 215

Heart disease, recent advances, 1944  
 Nov., 1338  
 rheumatic, 1943 Sept 1279, 1944  
 Sept., 1129  
 in large station hospital, 1944 Jan  
 127  
 seven common problems, manage-  
 ment, 1944 Sept., 1129  
 syphilitic, 1943 Sept., 1288 1944  
 Jan., 70  
 treatment, 1944 Nov., 1345  
 disordered action of, 1944 May, 569  
 effect of cigarette smoking on 1945  
 July, 949  
 of emotions on 1944 May 566  
 emergencies, 1943 Nov 1531 1945  
 Sept., 1154  
 in pediatric practice 1945 July 871  
 enlargement, in hypertension, 1943  
 Sept 1263  
 malignant hypertension with 1944  
 Sept. 1134  
 failure, acute in children, 1945 July  
 872  
 left sided 1945 Sept., 1159  
 congestive, 1943 Sept., 1283  
 mechanism 1944 Nov., 1343  
 mersalyl and theophylline orally  
 diuretic efficacy 1944 July 911  
 treatment, 1944 March, 381 382  
 with hypertension 1945 March  
 542  
 with normal rhythm, digitalis in,  
 1943 Jan., 146  
 digitalis in 1945 March 524  
 uses and abuses, 1943 Jan. 143  
 left ventricular acute 1943 Nov.,  
 1535  
 versus right ventricular failure,  
 1943 Jan., 121 135  
 right, with rapid enlargement of  
 liver 1944 Jan., 110  
 infarction with left ventricular failure  
 1943 Jan., 132  
 irregularities, electrocardiograms in  
 1945 May 590  
 irritable of soldiers, 1944 May, 569  
 decrease in World War II, 1944  
 May 560  
 lesions in hyperparathyroidism 1945,  
 March 395  
 mitralization 1944 Nov 1352  
 murmurs, in congenital heart disease  
 1944 Jan., 96 98 102  
 neurotic, 1944 May 570  
 position electrocardiogram and 1945  
 May 608  
 small, neurocirculatory asthenia due to  
 1944 May 577  
 structural abnormalities electrocardio-  
 grams in, 1945 May 595  
 tamponade, 1945 Sept 1158

- Heart, therapeutics, 1945 March, 423  
 Heat, application of, after amputations, 1943 July, 1110  
   in fibrositis, 1943 July, 906  
   radiant, in occlusive arterial diseases, 1943 July, 963  
   therapy, in rehabilitation, 1945 May, 787  
 Heating boot, 1943 July, 971  
   sleeve, 1943 July, 971  
 Heel, painful, 1943 July, 1141  
 Helium-oxygen therapy in bronchial asthma, 1944 March, 342, 348  
 Hemagglutination, 1944 Jan, 232  
 Hematocolpos, undiagnosed, in young girl, 1943 Jan, 19  
 Hematoma, subdural, 1945 Jan, 62  
   chronic, diagnosis, importance of, 1945 July, 1042  
 Hematuria, 1943 Nov, 1566  
 Hemerolopia, 1943 March, 355, 554  
 Hemiplegia, arthritis in, 1943 Sept, 1332  
   physical therapy in, 1943 July, 1015  
   treatment, 1944 March, 449  
 Hemoglobinuria, 1944 March, 379  
 Hemolysis, 1944 Jan, 232  
 Hemolytic anemia, acute acquired, 1945 May, 695  
   of newborn, Rh factor and, 1944 Jan, 244, 246  
   treatment, 1944 March, 378  
 Hemophilia, plasma in, 1945 Sept, 1085  
 Hemoptysis, 1945 July, 837  
 Hemorrhage, 1943 Nov, 1542  
   blood and blood substitutes in, 1943 Jan, 164  
   cerebral, 1943 Nov, 1554, 1944 March, 449  
   epidural, 1943 Nov, 1557  
   gastrointestinal, 1943 Nov, 1470, 1578  
   of functional origin, 1944 Sept, 1156  
   in liver damage, control of, 1945 March, 432  
   in peptic ulcer, 1943 Nov, 1578, 1944 March, 414  
   intracranial, convulsions of, 1945 July, 888  
   due to birth trauma, 1944 March, 448  
   obstetric emergencies associated with, 1943 Nov, 1601  
   of early pregnancy, 1945 July, 853  
   of late pregnancy, 1945 July, 855  
   of pregnancy, 1943 Nov, 1601  
   postpartum, 1943 Nov, 1610, 1945 July, 855, 858, Nov, 1537  
   pulmonary, idiopathic, 1945 July, 843  
   subarachnoid, 1943 Nov, 1554, 1557  
   subdural, 1943 Nov, 1557  
   tonsillar, postoperative, treatment, 1944 Sept, 1118  
   vaginal, 1943 Jan, 6  
 Hemorrhagic disease of newborn, vitamin K in, 1943 March, 377  
   tendency in vitamin C deficiency, 1943 March, 443  
   in vitamin K deficiency, 1943 March, 371  
 Hemorrhoidectomy, complications, prevention and management, 1943 Jan, 209  
 Hemothorax, 1945 March, 506, 510  
   in syphilitic aortic aneurysm, 1944 Jan, 76  
 Henoch's purpura, 1945 July, 880  
 Heparin in thrombosis and embolism, 1945 March, 431, July, 933  
 Herniation of intervertebral disk, 1945 Jan, 111  
 Hepatic See *Liver*  
 Hepatitis, epidemic, in military forces, 1944 Nov., 1355  
 Heredofamilial diseases, 1944 March, 451  
 Hermaphroditism, 1945 Nov, 1388  
 Hernia, diaphragmatic, dyspepsia in, 1944 July, 892  
   hiatus, significance in management of cardiac disorders, 1944 Jan., 108  
 Herpes rabbit vaccine X and F in von Economo's encephalitis, 1943 May, 648  
   zoster, 1944 March, 442  
 Hewitt pessary, 1943 Jan, 119  
 Hexestrol, 1943 Jan, 30, 1945 March, 435  
 Hexylresorcinol, vaporized, for disinfection of air, 1944 Nov, 1309  
 Heyrovsky operation for cardiospasm, 1944 May, 592  
 Hiatus hernia, significance in management of cardiac disorders, 1944 Jan, 108  
 Hip, arthritis, hypertrophic, physical therapy in, 1943 July, 920  
 Hippuric acid test of liver function, 1945 July, 977  
 Hirschsprung's disease, chronic diarrhea due to, 1944 Sept., 1195  
 Histaminase in nasal allergy, 1944 Nov, 1335  
 Histamine and mecholyl iontophoresis in rheumatoid arthritis, 1944 March, 319  
   in allergy, 1944 Nov, 1334  
   in Ménière's syndrome, 1944 Nov, 1324  
 Histamine-azoprotein in bronchial asthma, 1945 March, 460  
   in migraine, 1945 March, 438  
 Histoplasmosis, 1945 March, 337  
 Hodge pessary, 1943 Jan, 109, 111  
 Hodgkin's disease, 1944 Jan, 201  
   benign type, 1944 Jan, 201  
   malignant type, 1944 Jan, 204  
   reaction in leukemia, 1944 Nov, 1379  
   torulosis with, 1944 July 951, 953

- Hoffman sign in pyramidal tract lesions, 1945 Jan., 54
- Homoeroticism 1944 May 534
- Home deliveries, management 1945 Nov., 1525
- Homogenitalism, 1944 May 535
- Homosexuality, 1944 May, 535
- Hoover's sign 1944 July, 937
- Hormones adrenal, 1944 Sept 1237 1238
- clinical uses, 1944 Sept 1260
- assays of, 1945 Jan., 254
- follicle stimulating, 1943 Jan., 27 1944 Sept., 1234
- imbalance in leukemia, 1944 Nov., 1377
- in major disorders, 1944 Sept., 1248
- in carbohydrate metabolism 1943 March 319, 323
- in maintenance of chemical balance, 1943 Nov., 1615
- influences in peptic ulcer, 1944 March 411, Nov 1349
- interrelationships, 1944 Sept., 1232
- luteinizing 1943 Jan., 27 1944 Sept., 1234
- ovarian, 1943 Jan., 10, 29 1944 Sept., 1236
- pancreas, 1944 Sept., 1239
- parathyroid 1944 Sept. 1238 1264
- pituitary, 1943 Jan., 27 1944 Sept 1234 1235
- clinical uses, 1944 Sept., 1251 1266
- placental 1944 Sept. 1240
- preparations 1944 Sept., 1250
- testicular 1943 Jan., 33 1944 Sept 1237
- therapy See *Endocrine therapy*
- thyroid 1944 Sept., 1238
- Hospitalization, intramural, need for 1945 May, 812
- Hospitals, civilian, rehabilitation problem in, 1945 May 808
- rehabilitation possibilities in, postwar 1945 May 725
- Hostile-aggressive reactions in returned soldiers 1945 May 735
- Hostility 1945 Nov., 1512
- Hot packs in peripheral vascular disease 1943 July 951
- House dust, allergy to 1944 Nov., 1334
- Huddell's dye typing for differentiation of brucella 1943 May 700
- Huhner test for sterility 1943 Jan., 59
- Human being definition of 1944 March 452
- Hunner's ulcer 1945 Sept., 1205
- Hydatidiform mole 1943 Nov 1604 1945 July 854 856
- Hydradenitis suppurativa sulfonamides in 1944 July 846
- Hydrochloric acid in pernicious anemia 1944 Jan., 229 1945 Jan., 243
- Hydrophobia, 1943 Nov., 1514, 1944 Nov 1406
- immunization 1945 Sept., 1243
- Hydrops, congenital, Rh factor and 1944 Jan., 244 246
- Hydrothorax, 1945 March, 506, 510
- Hyoscine in prevention of motion sickness 1945 March 418
- Hypercalcemia, 1943 Nov 1629
- Hyperemesis gravidarum, 1945 Nov., 1436 1444
- Hyperesthesia hysterica, 1944 May 684 687
- Hyperimmune serum, 1945 Sept. 1085
- Hyperinsulinism 1945 July 1014
- Hyperirritability of digestive tract 1944 March 418
- Hyperkeratosis in early deficiency diseases, 1943 March 488
- in pellagra 1943 March, 386
- Hypermenorrhea 1944 Sept., 1219
- hormone therapy 1944 Sept., 1223
- Hyperparathyroidism 1944 March 472 1945 March 389
- primary diagnosis, 1945 July 1019
- Hyperpyrexia See *Fever therapy*
- Hypertension, 1943 Sept., 1257, 1944 Jan., 31
- arterial in congenital heart disease 1944 Jan., 102
- kidneys and clinical relationships 1945 March 535
- clinical concept of 1943 Sept., 1259
- drug therapy 1945 March 425
- emotional 1944 May 572
- essential 1943 Jan. 247 Sept., 1398 1944 Sept., 1141
- emotional factors in, 1944 May 573
- potassium thiocyanate in 1944 Sept., 1146
- sympathectomy for 1944 Sept. 1149
- in hypoplastic individuals 1944 May, 721
- in renal disease 1943 Jan., 247 Sept., 1260
- malignant, with cardiac enlargement 1944 Sept., 1134
- nervous, 1943 Sept., 1260
- ophthalmoscopic findings 1944 May 748
- pathogenesis 1944 May 724
- physiologic mechanisms with therapeutic implications 1943 Sept., 1397
- potassium sulfocyanate in 1943 Sept., 1268
- treatment 1943 Sept., 1268 1944 Sept., 1145
- Hypertensive cardiovascular disease, 1943 Jan., 237 238 239
- in pregnancy 1945 Nov., 1436 1440 1450



- Hypertensive heart disease with left ventricular failure, 1943 Jan, 125
- Hyperthyroidism, 1944 March, 469, 1945 July, 1013
- thiouracil in, 1945 March, 302, 433
- versus Graves' disease, 1944 March, 484
- Hypnosis in medicine, 1944 May, 639, 646
- phenomena of, 1944 May, 643
- technics of, 1944 May, 642
- Hypnotics in dermatology, 1945 Sept, 1105
- in insomnia, 1945 Jan, 187
- Hypocalcemia, electrocardiograms in, 1945 May, 613
- Hypochondriasis, 1944 May, 531, 699
- Hypochlorites, atomized, for disinfection of air, 1944 Nov, 1309
- Hypochlorous acid gas, disinfection of air with, 1944 Nov, 1310
- Hypoglycemia, cardiac manifestations, 1944 Nov, 1344
- obesity with, 1945 Sept, 1223
- spontaneous hyperinsulinism and, differentiation, 1944 July, 985
- Hypoglycemic crises in endocrine disorders, 1943 Nov, 1617
- Hypogonadism, male, hypoglycemic crises in, 1943 Nov, 1624
- severe suicidal tendencies in, 1943 Nov, 1630
- Hypomenorrhea, 1944 Sept, 1219
- hormone therapy, 1944 Sept, 1225, 1945 Jan, 260
- Hypoovarianism, 1944 March, 480
- Hypoparathyroidism, 1943 Nov, 1626, 1944 March, 471
- treatment, 1945 March, 434, 435
- Hypophysis See *Pituitary gland*
- Hypoplastic type, hypertension in, 1944 May, 721
- Hypoproteinemia, 1943 March, 305, 306, 307, 1945 Sept, 1083
- human serum albumin in, 1945 Sept, 1086
- in hepatic disease, 1943 March, 308
- nutritional, 1943 March, 307
- postoperative, 1943 March, 306
- serum transfusion in, 1943 Jan, 172
- wound healing and, 1943 March, 563
- Hypoprothrombinemia, 1943 March, 517
- Hypotension, neosynephrin hydrochloride in, 1945 March, 420
- Hypothalamus, physiology, 1944 Sept, 1233
- role of, in manic-depressive equivalents, 1944 March, 463
- Hypothermia in military practice, 1943 July, 1166
- Hypothyroidism, 1944 March, 467
- anemia of, 1944 March, 376
- arthralgia in, 1943 Sept, 1315
- obesity with, 1945 Sept, 1223
- Hysteria, 1944 May, 665, 682
- conversion, 1944 May, 532
- major, 1944 May, 689
- malinger and, differentiation, 1944 July, 935
- minor, 1944 May, 689
- traumatic sources, 1944 May, 682
- Hysteric zones, 1944 May, 684
- Hysteroid personality, 1944 May, 544, 545
- Hytakerol, 1943 Nov, 1627
- ICTERUS See also *Jaundice*
- gravis neonatorum, Rh factor and, 1944 Jan, 244, 246
- Ileitis, regional, sulfonamides in, 1944 July, 819
- Iliotibial bands, contracted, 1943 July, 1068
- Immersion foot, 1943 July, 1149
- hypothermia in, 1943 July, 1173
- Immune serum globulin, 1945 Sept, 1087
- in brucellosis, 1945 March, 359
- Immunization, active, against some common communicable diseases, 1945 Sept, 1238
- combined, 1945 Sept, 1250
- Immunotransfusion, 1943 Jan, 157
- Impetigo contagiosa, penicillin in, 1945 July, 836
- sulfathiazole in, topically, 1944 July, 847
- Indigestion, 1944 July, 891
- nervous, 1944 March, 418
- Industrial disability, respiratory disease as factor, 1944 Nov, 1293
- Industry, fatigue and exhaustion states in, 1945 May, 771
- Infant, newborn, immediate care of, 1945 Nov, 1531
- Infantile paralysis See *Poliomyelitis*
- Infants, diseases, sulfonamides in, 1944 July, 882
- emergencies of, 1943 Nov, 1520
- examinations, 1943 Nov, 1523
- feeding, 1943 Sept, 1355
- immunizations, 1943 Nov, 1521
- normal, care and feeding of, 1943 Nov., 1521
- premature, 1943 Nov, 1520
- miscellaneous, 1943 Nov, 1552
- Infections, chronic diarrhea in infants, due to, 1944 Sept, 1190
- confined air as vehicle, 1944 Nov, 1293
- generalized, ophthalmoscopic findings, 1944 May, 750
- Infectious diseases, symposium on, 1943 May, 601
- Influenza penicillin in, 1944 Sept, 1077
- sulfonamides in, 1944 Sept., 1077
- Influenzal infections, sulfamerazine in, 1943 Nov, 1456



- JACKET, Risser, in scoliosis, 1943 July, 1035
- Jacksonian epilepsy, 1945 Sept., 1115, 1122
- Jail fever, 1943 May, 775
- Janet test for sensory disturbance, 1944 July, 937
- Japanese encephalitis, 1943 Nov., 1513
- Japanese River Fever, 1944 Nov., 1464
- Jaundice, acholuric, familial type, 1945 July, 982
- catarrhal, in military forces, 1944 Nov., 1355
- cephalin-cholesterol flocculation test in, 1944 Nov., 1358
- hemolytic, congenital, Rh factor and, 1944 Jan., 244
- Jejunal transplant into stomach wall in peptic ulcer, 1944 Nov., 1350
- Joint strain, postural, 1943 Sept., 1311
- symptoms, specific diseases with, 1943 Sept., 1310
- Joints, disease of, degenerative, 1943 Sept., 1338
- hysteric, 1944 May, 687
- Jolly's myasthenic reaction, 1945 Jan., 129
- KALA-AZAR, 1943 Nov., 1492
- Kenny treatment of poliomyelitis, 1943 July, 883
- evaluation, 1943 Sept., 1345, 1348
- Kephriene hydrochloride, 1945 March, 420
- Kerandel's sign, 1943 May, 841
- Keratitis, interstitial, in riboflavin deficiency, 1943 March, 402, 405
- Keratconjunctivitis, epidemic, 1943 Nov., 1641
- phlyctenular, 1943 March, 556
- Keratomalacia, 1943 March, 357
- Keratosis, seborrheic, 1944 July, 969
- Ketohydroxyestrin, 1944 Sept., 1254
- 17-Ketosteroid test, 1944 Sept., 1242
- Kidneys, arterial hypertension and, clinical relationship, 1945 March, 535
- disease, in pregnancy, 1945 Nov., 1436
- treatment, 1943 Jan., 227, 1944 Sept., 1173
- unilateral, hypertension of, 1943 Sept., 1397
- emergencies, 1943 Nov., 1559
- functional tests, 1943 Sept., 1263
- values in health and disease, 1945 Sept., 1320
- in hypertension, 1943 Sept., 1263, 1264
- infarction of, 1943 Nov., 1553
- infections, nontuberculous, treatment, 1945 May, 571
- insufficiency, reversible and irreversible, 1944 March, 429
- lesions, in hyperparathyroidism, 1945 March, 394
- Kidneys, tuberculosis, 1944 Sept., 1185
- Kinases, 1943 March, 279
- Klumpke's paralysis in brachial plexus injuries, 1945 Jan., 19
- Koch's pressure dressing in burns, 1943 Sept., 1237
- Korotzin in hypermenorrhea, 1944 Sept., 1224
- Kraurosis vulvae, 1945 Nov., 1367
- Kyphosis, physical therapy, 1943 July, 1001
- LABOR, complications, 1945 Nov., 1536
- management at home, 1945 Nov., 1525
- psychiatric aspects, 1945 Nov., 1516
- single dose and continuous spinal anesthesia for, 1945 Nov., 1538
- third stage, complications, 1943 Nov., 1608
- Laboratory findings in blood and urine in health and disease, 1945 Sept., 1314
- procedures in gynecology and obstetrics, 1945 Nov., 1546
- Lacerations of cervix, 1943 Jan., 50
- Lameness, simulated, 1944 May, 700
- Lanatoside-C, 1943 Jan., 153, 1945 March, 424
- in heart disease, 1944 Nov., 1345
- Laryngeal diphtheria, 1945 July, 866
- Laryngology, recent advances, 1944 Nov., 1333
- Laryngotracheobronchitis, 1945 July, 864
- acute, in children, sulfonamides in, 1944 July, 887
- Larynx, carcinoma, 1944 March, 323
- diseases of, chronic, pitfalls in diagnosis and treatment, 1944 March, 322
- myasthenia, 1944 March, 326
- paralysis, due to tracheal tumor of probable syphilitic origin, 1944 March, 327
- Lawrence-Moon-Biedl syndrome, 1945 Sept., 1222
- Laxatives, avoidance, in functional disorders of digestive tract, 1944 March, 426
- Lead poisoning, ascorbic acid in, 1943 March, 578
- in children, 1945 July, 881
- sodium citrate in, 1945 March, 437
- Lederer's anemia, 1945 May, 702
- Leg stocking color preparation, thrombocytopenic purpura due to, 1944 Jan., 182
- Leishmaniasis, cutaneous, 1943 Nov., 1493
- mucocutaneous, American, 1943 Nov., 1493
- visceral, 1943 Nov., 1492
- Leprosy, 1943 Nov., 1484
- military aspects, 1944 Nov., 1484
- postwar problem of, 1945 July, 907

- Leukemia** 1944 Nov., 1376  
 acute, 1944 Jan., 188, Nov., 1385  
 chronic lymphocytic, 1944 Jan., 198, Nov., 1384  
 myelocytic, 1944 Jan., 194, Nov., 1383  
 hormonal imbalance in, 1944 Nov., 1377  
 subacute 1944 Jan., 189  
 symptoms 1943 Jan., 251  
 theories of origin 1944 Nov., 1376  
 treatment, 1943 Jan., 251 1944 Jan., 187 Nov., 1383  
**Leukocytes**, count, peripheral interpretation of, 1944 July 920  
**Leukoplakia** of vulva, 1945 Nov., 1368  
**Leukorrhea**, 1943 Jan., 3 43  
 hyperhormonal 1945 Nov., 1357  
 in children 1943 Jan., 48  
**Levator ani** test, 1943 Jan., 2  
**Light treatment** of rickets, 1943 March 366  
**Lightning pains** of tabes, treatment, 1944 March 445  
**Liniments** 1945 Sept., 1099  
**Lipophilia** 1943 March 336  
**Lipotropic substances** in cirrhosis of liver, 1945 March, 428 483 May 658  
**Lithiasis**, urinary following sulfonamides, 1943 Nov 1570  
**Liver** acute yellow atrophy, in pregnancy 1945 Nov., 1436 1445  
 biopsy, by aspiration, 1945 March, 365  
 cirrhosis See *Cirrhosis of liver*  
 damage to hemorrhage in control of, 1945 March 432  
 diseases, diet as factor 1945 March 276, 427 484  
 hypoproteinemia of 1943 March, 308  
 malnutrition due to 1943 March 525 573  
 dysfunction constitutional 1945 July 982  
 enlargement, rapid, with right heart failure 1944 Jan., 110  
 functional tests, 1945 July 973  
 composite, 1945 March 363  
 values in health and disease, 1945 Sept., 1319  
 therapy in nutritional macrocytic anemia 1943 March 479  
 in pernicious anemia, 1943 March 477, 1944 Jan., 227 March 374 1945 Jan. 242  
 in sprue, 1943 March 462  
 in subacute combined degeneration 1943 March 427  
**Lobar pneumonia**. See *Pneumonia*  
**Lobectomy** in tuberculosis, 1945 March 451  
**Lobotomy** prefrontal, in psychoses, 1945 Sept., 1232  
**Lockjaw** See *Tetanus*  
**Lordosis**, physical therapy, 1943 July, 1001  
**Lotions**, dermatologic, 1945 Sept., 1097  
**Lumbago**, etiology, 1945 May, 568  
**Lumbar puncture** in meningitis, 1943 Nov., 1500 1945 Sept., 1264  
**Lumbosacral strain** acute 1943 July 1066  
**Lung abscess** emergency aspects, 1945 July, 841  
 multiple staphylococcal bacteremia complicating penicillin in 1944 Sept 1035  
 surgical indications and treatment, 1945 Sept 1288  
 carcinoma emergency aspects, 1945 July 842  
 primary surgical indications and treatment 1945 Sept., 1282  
 cystic disease, emergency aspects, 1945 July 845  
 diseases, chronic with constriction in bronchial passageway, 1944 March 348  
 edema of acute emergency aspects, 1945 July 837  
 in congestive heart failure 1944 March 386  
 resection in tuberculosis, 1945 March 451  
 tuberculosis. See *Tuberculosis pulmonary*  
**Luteinizing hormone** 1943 Jan 27 1944 Sept., 1256  
 in menstrual disorders, 1944 Sept., 1225  
**Luxation** 1943 March 335  
**Lymph scrotum** 1943 May 864  
**Lymphangitis**, regional, sulfonamides in 1944 July 845  
**Lymphedema** prevention 1943 July 958  
**Lymphocytic choriomeningitis**, 1943 Nov., 1517  
 benign 1945 Jan 36  
**Lymphogranuloma venereum** 1945 May 663 Nov 1369  
 conjunctivitis due to sulfonamides in 1944 July 794  
 diagnosis 1945 May 677  
 extragenital 1945 May 675  
 treatment 1945 May 682  
 ulcerative colitis due to sulfonamides in 1944 July 815  
**Lymphopathia venereum** 1945 Nov., 1369  
**Lymphorrhoids** in lymphogranuloma venereum 1945 May 670 671  
**MACROCYTIC** anemias, nutritional 1943 March 467, 479

- Madura foot, 1943 July, 1150  
 Magnesium sulfate in Mènière's syndrome, 1944 Nov, 1324  
     in paroxysmal tachycardia, 1945 March, 426  
 Maladjustment, transitory, in soldiers, reconditioning in, 1945 May, 751  
 Malaria, 1943 May, 615, 617, Sept, 1417, Nov, 1477, 1944 Nov, 1437, 1458  
     benign, 1943 Sept, 1418  
     control measures, 1943 May, 629, Sept, 1422, Nov, 1478  
     diagnosis, 1943 Sept., 1426, 1944 Nov, 1453, 1455, 1458  
     parasites of, 1943 May, 621, Sept, 1418, 1944 Nov, 1438  
     pathology, 1944 Nov, 1439  
     pernicious or malignant, 1943 Sept, 1419  
     practical considerations, 1944 Nov, 1437  
     postwar problem of, 1945 July, 902  
     prophylaxis and treatment, 1943 May, 626, 627, Sept, 1423, Nov, 1479  
     reconditioning the patient, 1945 May, 760  
     sternal puncture in, 1943 Sept, 1426  
     symptoms, 1943 May, 624, 1944 Nov, 1440  
     time factor in military operations, 1943 Sept, 1425  
     war, 1943 May, 615, Sept, 1417  
 Male climacteric, 1944 March, 483  
 sex hormone See *Androgens*  
 Malignant peptic ulcer, 1944 March, 416  
 Malingering, 1944 May, 699, July, 928  
     foot disabilities and, 1943 July, 1151  
     neuropsychiatric aspects, 1944 July, 928  
     of insanity to escape criminal responsibility, 1945 Jan, 205  
 Malnutrition, 1943 March, 567  
     serum transfusion in, 1943 Jan, 172  
 Malta fever See *Brucellosis*  
 Mammary gland, physiology, 1944 Sept, 1239  
 Mandelic acid in pyelonephritis, 1943 Nov, 1561  
     in urinary tract infection, 1944 Sept, 1184, 1945 May, 574, 576  
 Manganese as nutrient, 1943 March, 284  
 Manic-depressive constitution, neuroses related to, 1944 March, 452  
     equivalents, 1944 March, 457  
 Manipulative therapy for backache, 1943 July, 1071  
 Mapharsen in cardiovascular syphilis, 1944 March, 305  
     in early syphilis, 1944 March, 294, 298  
     in relapsing fever, 1943 May, 743  
 March foot, 1943 July, 1148  
     hemoglobinuria, 1944 March, 379  
 Marriage, preparation for, physician's role, 1945 Nov, 1346  
 Masklike expression in pellagra, 1943 March, 391  
 Massage in after-treatment of amputations, 1943 July, 1110  
     in fibrosis, 1943 July, 906  
     in rehabilitation, 1945 May, 787  
 Mastoiditis, acute, sulfonamides in, 1944 July, 799  
 Measles, complications, sulfonamides in, 1944 July, 888  
     in infants, 1943 Nov, 1527  
 Mebaral in epilepsy, 1945 Sept, 1122  
 Mecholyl, effects on electrocardiogram, 1945 May, 614  
     in bronchial asthma, 1945 March, 459  
     iontophoresis in paroxysmal tachycardia, 1943 Nov, 1539  
     in rheumatoid arthritis, 1944 March, 319  
 Median nerve injuries, 1945 Jan, 11  
 Median-ulnar nerve injuries, 1945 Jan, 18  
 Medical emergencies on home front, symposium on, 1943 Nov, 1447  
     symposium on, 1945 July, 833  
 Medicine, recent advances, symposium on, 1944 Nov, 1293  
 Medullary tractotomy for facial pain, 1945 Jan, 84  
 Megacolon, congenital, chronic diarrhea due to, 1944 Sept., 1195  
 Megakaryocytes, bone marrow, in thrombocytopenic purpura, 1944 Jan, 158, 167  
 Meigs' syndrome, pleural effusion in, 1945 March, 509, 512  
 Melancholia, involution, 1945 Nov., 1522  
 Melanocarcinoma, 1944 July, 971  
 Melano-epithelioma, 1944 July, 971  
 Mehtene in brucellosis, 1943 May, 716  
 Membrana tympani, perforations, 1944 March, 334  
 Menge pessary, 1943 Jan., 116, 119  
 Mènière's syndrome, treatment, 1944 Nov, 1323  
 Meningismus in infants, 1943 Nov, 1530  
 Meningitis, 1943 Nov, 1496  
     acute, emergency treatment, 1945 July, 895  
     aseptic, acute, 1943 Nov, 1517  
     bacillus coli, 1945 Sept, 1268  
     bacterial, acute, sulfonamides in, 1944 July, 869  
     coma of, emergency treatment, 1945 July, 893  
     diagnosis, 1945 Sept, 1260  
     hemolytic streptococcus, 1943 Nov, 1503  
     in infants, 1943 Nov, 1529  
     influenzal, 1943 Nov., 1505

- Meningitis, influenzal, serum therapy, 1945 Sept., 1263, 1266  
sulfamerazine in 1943 Nov., 1456  
sulfonamides in 1944 July, 872  
lumbar puncture in 1945 Sept., 1264  
lymphocytic, benign 1945 Jan., 36  
meningococcal, 1943 Sept., 1204, Nov., 1496  
serum therapy 1943 Nov., 1502  
1945 Sept., 1263  
sulfamerazine in 1943 Nov., 1454  
sulfonamides in, 1943 Sept., 1204  
1205 1253, Nov., 1454 1500  
1944 July, 869 872 1945 Sept., 1263 1310  
pneumococcal, 1943 Nov., 1504  
penicillin in 1945 May 585  
sulfonamides in 1944 July 870 872  
staphylococcal, 1943 Nov., 1506  
penicillin in, 1943 Sept., 1264 1267  
sulfonamides in, 1944 July, 870  
streptococcal penicillin in 1945 Sept., 1264 1267  
sulfonamides in, 1944 July 870 872  
torula 1944 July 951, 952  
treatment, 1945 Sept., 1259 1262  
tuberculous, 1945 Sept., 1267  
Meningococcal infections, sulfamerazine in, 1943 Nov., 1454  
sulfonamides in 1944 July 869 872  
Meningococcemia 1943 Sept., 1205  
Menometrorrhagia, 1944 Sept., 1222  
Menopause, 1945 July 1015 Nov., 1416  
arthralgia of, 1943 Sept., 1316, 1945 Sept., 1274  
endocrine therapy 1943 Jan., 39 1945 Nov., 1406  
male, 1945 July, 1015  
treatment 1943 Jan. 10 1944 March 482 1945 Nov., 1420  
Menorrhagia, 1943 Jan., 37, 1945 Nov., 1383  
hormone therapy 1943 Jan., 37 Sept., 1378 1945 Jan., 259 261 264 266 Nov., 1385  
Menstrual calendar records, 1943 Jan., 63  
Menstruation disorders of, 1944 Sept., 1217  
diagnostic aids 1945 Jan., 252  
endocrine therapy, 1945 Jan., 251  
uses and abuses, 1945 Nov., 1400  
functional 1945 Nov 1375  
hormone therapy 1943 Sept 1373, 1945 Nov., 1375  
psychiatric aspects 1945 Nov., 1519  
treatment, 1944 Sept., 1222  
Menstruation, 1945 Nov 1375  
Mental alienation, Kenny concept 1943 July 889  
disease criminal responsibility and 1945 Jan., 195  
Mental disease, electric convulsive therapy 1943 July, 1019  
growth, levels of, 1944 May 530  
hygiene of chronic disease, 1944 March, 434  
retardation criminal responsibility and, 1945 Jan., 208  
symptoms in hysteria, 1944 May, 688  
in neurasthenia, 1944 May, 675  
produced by anoxia, 1944 May, 704  
Mercupurin as diuretic, 1945 March, 424  
Mercurial diuretics in congestive heart failure, 1944 March, 385  
intravenous, toxic effects, 1944 Nov., 1346  
Mersalyl and theophylline orally in congestive heart failure, diuretic efficacy, 1944 July, 911  
Mesenteric thrombosis and embolism, 1943 Nov., 1552 1944 May, 730  
Metabolic arthritis, 1943 Sept., 1328  
diseases, abdominal symptoms, 1943 Nov 1474  
Metabolism altered as cause of deficiency states 1943 March 529  
Methenamine in urinary tract infections, 1945 May 574 575  
Methionine in cirrhosis of liver, 1945, March 429 484  
Methyl testosterone 1944 Sept., 1259  
Metrazol shock therapy in psychosis, 1945 Sept., 1232  
Metritis puerperal 1945 Nov., 1487  
Metropathia haemorrhagica, 1944 Sept., 1222  
Metrorrhagia, hormone therapy 1943 Sept., 1378  
Meulengracht diet in hemorrhagic peptic ulcer, 1943 Nov., 1582  
Microsporon infections, 1945 March, 323  
Middle ear inflammation See *Otitis media*.  
Midsystolic click in acute rheumatic heart disease 1944 Jan., 129  
Migraine, 1944 March 439  
abdominal, 1944 May 733  
histamine-azoprotein in, 1945, March, 438  
suicidal tendencies in 1943 Nov., 1630  
Military personnel nutrition as it affects, 1943 March 581  
physical medicine, symposium on 1943 July 1024  
Minerals, function in nutrition 1943 March 283  
Miosis, 1944 May 746  
Miscarriage See *Abortion*  
Mite bites in soldiers in tropics, 1944 Nov., 1538  
typhus, 1944 Nov., 1464  
Mitral stenosis, 1944 Jan., 47  
pregnancy and, 1944 Jan., 51

- Mitral stenosis, with right ventricular failure, 1943 Jan, 121
- Moles, benign and malignant, differentiation and treatment, 1944 July, 968  
blue, 1944 July, 973  
hydatidiform, 1943 Nov, 1604, 1945 July, 854, 856  
pigmented, 1944 July, 968  
vascular, 1944 July, 974
- Moncheberg calcification, 1944 May, 724
- Monilia albicans, infections with, 1945 March, 323, 328
- Moniliasis, vaginal, 1943 Jan, 5, 46, 1945 Nov, 1360
- Monoacetylmorphine, 1945 March, 418
- Monocaine for local anesthesia, 1945 March, 419
- Moods, instability of, 1944 March, 464
- Morphine in convalescence, 1945 Sept, 1212  
in coronary thrombosis, 1944 Jan, 8
- Motion sickness, treatment, 1945 March, 418
- Motor disorders, chronic, management, 1944 March, 437  
simulated, 1944 July, 936
- Mottled enamel, 1944 Nov, 1430
- Mouth lesions in pellagra, 1943 March, 388, 548  
in riboflavin deficiency, 1943 March, 401, 550  
in sprue, 1943, March, 454  
ulcers, sulfonamides in, topically, 1944 July, 848  
wash in pernicious anemia, 1945 Jan, 245
- Mucous colitis, 1944 March, 418
- Multiple sclerosis, treatment, 1944 March, 446
- Mumps, 1943 Nov, 1529
- Muscle reeducation following nerve suture, 1943 July, 1096
- Muscular action, basic principles in, 1943 July, 925  
atrophy after nerve damage, 1943 Sept, 1404  
spinal, progressive, 1944 March, 449  
incoordination, Kenny concept, 1943 July, 889  
spasm, Kenny concept, 1943 July, 888  
weakness, neurasthenic, 1944 May, 676, 681
- Musculocutaneous nerve injuries, 1945 Jan, 23
- Myasthenia gravis, diagnostic tests, 1945 Jan, 128, March, 422  
management, 1945 Jan, 126, 129  
treatment, 1944 March, 438  
advances in, 1945 March, 421  
laryngis, 1944 March, 326  
prosthigmine in, 1944 Nov, 1333
- Myasthenic reaction of Jolly, 1945 Jan, 129
- Mycology, medical, 1945 March, 323
- Mydrnasis, 1944 May, 746
- Myelitis, ascending, 1943 Nov, 1516  
treatment, 1944 March, 437
- Myelopathy, 1944 March, 437
- Myocardial infarction, restriction of activity in coronary occlusion in relation to, 1945 March, 405
- Myocarditis, Fiedler's, electrocardiogram in, 1945 May, 606
- Myoclonic jerks, 1945 Sept, 1117, 1123
- Myxedema, 1944 March, 467, 1945 July, 1012  
pituitary, 1944 Nov, 1386  
in children, 1944 Nov, 1390
- NARCISSISM, 1944 May, 533
- Narcolepsy, 1944 March, 442  
in children, 1945 July, 894
- Narcosis, anoxia and, 1944 May, 713
- Narcosynthesis in war neurosis, 1945 May, 737
- Nasal allergy, 1944 Nov, 1334
- Nasopharyngeal conditions, new treatment, 1944 Nov, 1331
- Nasopharynx, gonadal relationships, 1944 Nov, 1329  
hyperplasia, conductive deafness and, 1945 Sept, 1251
- Navy, physical therapy in, symposium on, 1943 July, 1024  
respiratory infections, in tropical S Pacific, 1944 Nov, 1418
- Neck, injuries and infections, physical therapy in, 1943 July, 919  
painful, 1945 May, 568
- Needle liver biopsy, 1945 March, 365
- Neoantimosan in schistosomiasis, 1943 May, 859
- Neoarphenamine in aortic syphilis, 1944 March, 305  
in early syphilis, 1944 March, 294  
in relapsing fever, 1943 May, 743  
in urinary tract infections, 1945 May, 577
- Neoprontosil in ulcerative colitis, streptococcal, 1944 July, 814
- Neostigmine in fasciculation, 1945 March, 422  
in myasthenia gravis, diagnostic, 1945 March, 422  
therapeutic, 1945 March, 421  
in poliomyelitis, 1945 March, 423  
in rheumatoid arthritis, 1945 March, 423
- Neosynephrin hydrochloride, uses, 1945 March, 420  
in bronchial asthma, 1944 March, 346  
in chronic pulmonary diseases with bronchial constriction, 1944 March, 349

- Nephritis, acute 1943 Nov., 1571  
     hemorrhagic, specific therapy, 1945  
     Sept., 1173  
     chronic diffuse management, 1945  
     Sept. 1184  
     differential diagnosis, 1945 July, 990  
     in children, 1945 July, 874  
     treatment, 1943 Jan., 227 1944 Sept.,  
     1173
- Nephrocalcinosis in hyperparathyroidism  
 1945 March, 394
- Nephrosis in children 1945 July 874  
 management 1945 Sept 1185  
 serum transfusion in, 1943 Jan, 173  
 testosterone in 1945 March 436
- Nephrotic crisis 1945 Sept., 1190  
 edema 1944 Sept., 1181  
 syndrome, treatment, 1944 Sept., 1186
- Nerve grafts, 1945 Jan., 27
- Nerves, peripheral, injuries, diagnosis and  
     surgical treatment 1945 Jan., 9  
     physical therapy in 1943 July, 1097  
     suture of physical therapy following  
     1943 July, 1091
- Nervous disease, organic origin in appar-  
     ent functional cases 1945 Jan., 30  
     indigestion 1944 March 418  
     system, autonomic, therapeutics, 1945  
     March 419  
     central affections of in aged physical  
     therapy 1943 July 1015  
     syphilis of 1944 March 303  
     therapeutics, 1945 March 417  
     chronic disease, management of 1944  
     March, 434  
     diseases of abdominal symptoms,  
     1943 Nov., 1473
- Nervousness in nutritional deficiency  
 1943 March 434
- Neuralgia, trigeminal 1945 Jan., 73  
     atypical, 1945 Jan., 85  
     symptomatic, 1945 Jan 75
- Neurasthenia 1944 May 533 665 672  
     traumatic sources 1944 May 673
- Neurasthenoid personality, 1944 May  
 546
- Neuritis, alcoholic, 1943 March 424  
     multiple See *Polymyositis*  
     nutritional 1943 March 419  
     optic, and brain tumors papilledema in  
     1944 July 957  
     retrobulbar vitamin therapy, 1943  
     March 559  
     treatment 1944 March 447
- Neurocirculatory asthenia 1944 May  
 569, 666 Sept., 1133  
     due to small heart, 1944 May 577  
     electrocardiogram in, 1945 May 617  
     in soldiers overseas 1944 Nov 1509
- Neurogenic bladder 1943 Nov., 1566
- Neurologic emergencies nonsurgical in  
 children, 1945 July 886
- Neurologic emergencies, of nicotinic acid  
     deficiency, 1943 March, 390  
     of thiamine deficiency, 1943 March,  
     415
- Neuromuscular apparatus, therapeutics,  
 1945 March, 421
- Neuropathic arthritis 1943 Sept., 1331
- Neuropathy 1944 March, 447
- Neuropsychiatric aspects of malingering,  
 1944 July 928  
     diseases, symposium on 1945 Jan., 1
- Neuroses anxiety 1944 May 672  
     manifested by cardiovascular symp-  
     toms, 1944 Nov., 1509  
     by gastrointestinal symptoms, 1944  
     Nov., 1541
- electrotherapy 1944 March, 462, 465  
 gastrointestinal, 1944 Nov., 1541  
 in combat crews overseas, 1945 May,  
 731
- in returned soldiers 1945 May, 733  
 organ 1944 May 532  
 plus malingering, 1944 May 702  
 psychopathology of 1945 Nov 1511  
 related to the manic-depressive constitu-  
 tion 1944 March 452
- sexual factors 1943 Nov 1639  
 traumatic, 1944 May 663  
     decrease in, in World War II 1944  
     May, 560  
     differential diagnosis 1944 May 699  
     military experience 1944 May 669  
     nomenclature and etiology 1944  
     May 663  
     prognosis 1944 May, 693  
     treatment 1944 May 697  
     war 1945 May, 729
- Neurosurgery, fibrin film and foam in  
 1945 March, 433
- Neurosyphilis, 1944 March 303  
     treatment, 1945 Sept., 1231
- Neurotic heart, 1944 May 570
- Neurotics, defined 1944 March 455
- Neurotomy retrogasserian, classical for  
     facial pain, 1945 Jan., 80  
     posterior for facial pain 1945 Jan.,  
     83
- Neutralization tests for arthropod borne  
     virus encephalitides, 1943 May, 642
- Nevus blue, 1944 July 973  
     pigmentosus, 1944 July 968  
     vasculosus 1944 July 974
- New developments in medicine symposium  
 on, 1945 March 273
- Newborn erythroblastosis in Rh factor  
     and 1944 Jan 240 258  
     hemorrhagic disease vitamin K in 1943  
     March 377  
     immediate care of 1945 Nov., 1531
- Niacin dosages 1945 Sept. 1302
- Nicotinamide in arthralgia of vitamin B  
     deficiency 1943 Sept., 1319



- Nicotine, effects on electrocardiogram, 1945 May, 612  
 intravenous administration, effect on heart and peripheral blood vessels, 1945 July, 949
- Nicotinic acid deficiency See *Pellagra*  
 dietary requirements, 1943 March, 294  
 effects on electrocardiogram, 1945 May, 614  
 enzyme relationships, 1943 March, 280  
 in chemotherapy, 1943 March, 578  
 in deficiency diseases, 1943 March, 274  
 in Ménére's syndrome, 1944 Nov., 1324  
 in pellagra, 1943 March, 394  
 in radiation sickness, 1943 March, 578  
 in Vincent's infection, 1944 Nov., 1332
- Night blindness, 1943 March, 355, 554  
 palsy, 1944 July, 945
- Nitroglycerin in angina pectoris, 1943 Sept., 1286, 1944 Jan., 27
- Nocardia asteroides, infection with, 1945 March, 340
- Nose, diseases of, chronic, 1944 March, 330  
 new treatments, 1944 Nov., 1328  
 sulfonamides in, 1944 July, 797  
 local use, 1944 July, 800  
 treatment, 1944 Sept., 1108  
 fracture, treatment, 1944 Sept., 1121  
 furuncle, with cellulitis of face, penicillin in, 1944 Sept., 1037  
 lesions, in riboflavin deficiency, 1943 March, 402  
 physiology, applied, 1944 Sept., 1110
- Nosebleed, 1944 Sept., 1116
- Nutrients, biological significance, 1943 March, 277  
 foods as sources, 1943 March, 287
- Nutrition, adenylic acid in, 1943 March, 483  
 eye lesions and, 1943 March, 553  
 in practice of medicine, 1943 March, 567  
 in pregnancy, 1943 March, 537  
 in rehabilitation, 1945 May, 794  
 military aspects, 1943 March, 581  
 symposium on, 1943 March, 273  
 teeth and, 1943 March, 545  
 wound healing and, 1943 March, 561
- Nutritional anemias, treatment, 1944 March, 376  
 deficiencies, central nervous system manifestations, 1943 March, 431  
 neuritis of, 1943 March, 419  
 subacute combined degeneration of spinal cord in, 1943 March, 425
- Nutritional deficiency diseases See *Deficiency diseases*  
 macrocytic anemia, 1943 March, 467, 479
- Nyctalopia, 1943 March, 355, 554
- OBER reaction, 1943 July, 1068
- Obesity, 1943 March, 327  
 in children, 1945 Sept., 1217  
 treatment, 1945 Sept., 1226
- Obsessional thinking, 1944 March, 456
- Obstetric emergencies, 1943 Nov., 1596  
 associated with hemorrhage, 1943 Nov., 1601
- Obstetrics, chemotherapy in, 1944 July, 827  
 laboratory procedures in, 1945 Nov., 1546  
 nonsurgical emergencies in, 1945 July, 848  
 psychiatric aspects, 1945 Nov., 1508, 1514  
 Rh factor in, 1944 Jan., 240, 254  
 symposium on, 1945 Nov., 1343
- Occupational therapy after amputations, 1943 July, 1120  
 in rehabilitation, 1945 May, 788  
 in the war, 1943 July, 1154  
 psychiatric value, 1943 July, 1161  
 value in maintenance and restoration of functions of joints and muscles, 1943 July, 1156
- Octofollin, 1945 March, 435
- Ocular See *Eyes*
- Office gynecology, symposium on, 1943 Jan., 1
- Oiling as dust-suppressive measure, 1944 Nov., 1312
- Oils, dermatologic, 1945 Sept., 1100
- Ointments, 1945 Sept., 1100
- Oligomenorrhea, 1944 Sept., 1218, 1220  
 hormone therapy, 1944 Sept., 1225
- Oliguria, acute, treatment, 1943 Jan., 242  
 in infants and children, 1945 July, 874
- Omentopexy in cirrhosis of liver, 1945 March, 281
- Onierophrenia, 1945 Jan., 162
- Operational fatigue, 1945 May, 729
- Ophthalmia, gonorrheal, in child, 1943 Jan., 80  
 sulfonamides in, 1944 July 793, 886
- Ophtha'modynamometry, 1944 May, 744
- Ophthalmologic aids, medical, in civilian and military general practice, 1944 May, 742  
 examinations, written, experience with 1943 Sept., 1409
- Ophthalmology, sulfonamides in, 1944 July, 789
- Ophthalmoscopic accessories, 1944 May, 746  
 findings in disease, 1944 May, 747

- Ophthalmoscopy technic, 1944 May, 744  
 Opisthotonos, hysteric, 1944 May, 690  
 Oppenheim's sign in pyramidal tract lesions, 1945 Jan., 52  
 Opsonocytophagic index in brucellosis, 1943 May 712 1945 March 354  
 Optic atrophy primary, syphilitic, surgical treatment, 1944 March 304  
     tabetic, treatment, 1944 March 446  
     neuritis and brain tumors, papilledema in 1944 July, 957  
 Organ neurosis, 1944 May, 532  
 Organic origin of apparent functional nervous disease, 1945 Jan., 30  
     tradition in medicine, 1943 Nov., 1635  
 Oriental sore, 1943 Nov., 1493  
 Orthopedics, physical therapy in 1943 July 913  
 Oscillating bed, 1943 July 985  
 Osteitis fibrosa cystica generalisata, 1945 March, 389 395  
 Osteoarthritis, 1943 Sept., 1338 1945 Sept. 1278  
     etiology, environmental factors, 1945 May 567  
     physical therapy 1943 July 1008  
 Osteomalacia, 1943 March 515  
 Osteomyelitis, acute hematogenous, with staphylococcal bacteremia, penicillin in, 1944 Sept., 1031  
     of femur chronic, penicillin in 1944 Sept., 1038  
 Osteoporosis, senile, physical therapy 1943 June 1010  
 Otitis, chronic, 1944 March 334 336  
     media, acute, in children sulfonamides in, 1944 July 887  
     treatment, 1944 Sept., 1125  
     chemotherapy 1944 July 799 801  
     in infants, 1943 Nov., 1525  
 Otolaryngology problems in treatment by general practitioner 1944 Sept. 1108  
     recent advances, 1944 Nov., 1310  
     sulfonamides in 1944 July 797  
     local use 1944 July 801  
 Otorrhea, chronic, 1944 March 334  
 Ouabain 1943 Jan., 153, 1945 March 424  
 Ovary dermoid tumor pregnancy complicating in young girl 1943 Jan., 23  
     function vaginal smears for 1945 Nov., 1549  
     hormones, 1943 Jan., 1029  
     hypofunction 1944 March 480  
     physiology 1944 Sept. 1236  
 Overstrain treatment in hypertension 1943 Sept., 1272  
 Ovulation disorders associated with hormone therapy 1943 Sept., 1382  
     timing, by basal temperature graphs, 1943 Nov 1425  
 Oxygen pressure in atmosphere, effect on emotional control, 1944 May, 704  
     therapy in bronchial spasm of acute in sections, 1944 March, 349  
     in coronary thrombosis, 1943 Nov., 1535 1944 Jan., 8  
     in left ventricular failure, 1943 Nov., 1537  
     in status asthmaticus, 1944 March, 345  
 Oxygen helium therapy in bronchial asthma, 1944 March, 342, 351  
 Pain abdominal, acute diagnosis 1943 Nov 1456  
     anginal, 1944 Jan., 17  
     facial, neoplasia as cause, 1945 Jan., 91  
     relief of, 1945 Jan., 73  
     symptomatic, 1945 Jan., 87  
     gastrointestinal, of functional origin, 1944 March 419  
     hysteric, 1944 May, 687, 698  
     in joints, 1943 Sept., 1311  
     in neurasthenia, 1944 May, 674  
     intractable, chordotomy for, 1945 Jan., 98  
     precordial, differential diagnosis, 1945 March 513  
     radicular 1943 July, 994  
     physical therapy for 1943 July, 1001  
     relief of, in peptic ulcer 1944 March 406  
     simulated 1944 May, 700, July, 935  
 Paleness, emotions and, 1944 May 572  
 Pancreas, disturbances 1945 July 1014  
     physiology 1944 Sept., 1239  
 Pancreatic fibrosis, chronic diarrhea in infants due to 1944 Sept., 1198  
     insufficiency pancreatic enzyme in 1945 March 429  
 Pancreatitis, 1943 Nov., 1472 1587  
     acute, electrocardiogram in 1945 May 607  
 Papaverine in coronary thrombosis, 1944 Jan 6  
 Papilledema in optic neuritis and in tumor of brain 1944 July, 957  
 Para aminobenzoic acid enzyme relationships, 1943 March, 283  
 Paracentesis in cirrhosis of liver 1945 March 281  
 Paraffin boot in peripheral vascular disease 1943 July 989  
 Paraldehyde in bronchial asthma, 1944 March, 345  
 Paralysis agitans, treatment, 1944 March 443  
     cerebral of children treatment, 1944 March 448  
     rehabilitation in 1945 May 792, 819

- Paralysis, Erb's, 1945 Jan, 19  
familial periodic, thyroid in, 1945  
March, 422  
hysteric, 1944 May, 685, 698  
infantile See *Poliomyelitis*  
Klumpke's, 1945 Jan, 19  
simulated, 1944 May, 701  
sleep, 1944 July, 945  
spastic, cerebral, physical therapy in,  
1943 July, 914
- Parametritis, puerperal, 1945 Nov, 1488
- Paranasal sinuses See *Sinuses*
- Paraphimosis in children, 1945 July,  
877
- Parasites, intestinal, in children, 1944  
Sept, 1191
- Parasympathomimetic drugs, 1945 March,  
421
- Parathyroid extract, therapeutic test, 1944  
Sept, 1248  
fever, immunization, 1945 Sept, 1245  
hormone, 1944 Sept, 1238, 1264  
insufficiency, 1945 July, 1013
- Parathyroids, diseases of, 1944 March,  
470, 1945 March, 389
- Paredrine, uses, 1945 March, 420
- Paredrinol, uses, 1945 March, 420
- Parkinsonism, postencephalitic, 1943  
Nov, 1509  
treatment, 1944 March, 443
- Parotitis, epidemic, electrocardiogram in,  
1945 May, 607
- Paroxysmal tachycardia, 1943 Nov,  
1537, 1945 Sept, 1154, 1156
- Passive dependent reactions in returned  
soldiers, 1945 May, 734  
vascular exercises, 1943 July, 973
- Pastes, dermatologic, 1945 Sept, 1098
- Pasteur treatment, 1943 Nov, 1516, 1944  
Nov, 1411, 1412
- Pasteurella pestis, 1943 May, 750, 758
- Patek's diet in cirrhosis of liver, 1945  
March, 276
- Patellar clonus in pyramidal tract lesions,  
1945 Jan, 57
- Patency, tubal, Rubin test, 1943 Jan,  
9, 61
- Patent ductus arteriosus, 1944 Jan, 98  
102  
surgical treatment, evaluation, 1944  
March, 388
- Patulin in common cold, 1944 Nov,  
1328
- Pavaex therapy in occlusive arterial dis-  
ease, 1943 July, 973
- Pectin in thrombocytopenic purpura,  
1944 Jan, 169
- Pediatric emergencies 1943 Nov, 1520
- Pediatrics, sulfonamides in, 1944 July,  
882
- Pellagra, 1943 March, 379  
alcoholic, 1943 March, 393
- Pellagra, central nervous system manifes-  
tations, 1943 March, 431  
diet in, 1945 May, 803  
early, 1943 March, 495  
laboratory diagnosis, 1943 March, 501  
mouth lesions, 1943 March, 389, 548  
pathology, 1943 March, 513  
psychoses in, 1943 March, 391, 432  
recurrent, 1943 March, 392  
sine pellagra, 1943 March, 393  
treatment, 1943 March, 274, 394
- Pelvic cellulitis, puerperal, 1945 Nov,  
1488  
examination, 1945 Nov, 1346  
inflammatory disease after irradiation,  
chemotherapy in, 1944 July, 835  
peritonitis, puerperal, 1945 Nov, 1490  
tilt roentgenogram, 1943 July, 1032
- Penicillin in anthrax, 1945 July, 835  
in burns infection, 1945 July, 836  
in carbuncles, 1945 July, 836  
in cavernous sinus thrombosis, 1945  
July, 894  
in cellulitis, 1945 May, 584, July, 836  
in dermatology, 1945 Sept, 1107  
in early syphilis, 1944 March, 302  
in erysipelas and erysipeloid, 1945 July,  
836  
in furunculosis, 1945 July, 836  
in glomerulonephritis, 1945 May, 582  
in gonorrhea, 1944 March, 507  
in women, sulfonamide resistant,  
1944 July, 835  
in hemolytic streptococcus infections,  
1943 Sept, 1203, Nov, 1504  
in impetigo contagiosa, 1945 July, 836  
in influenza, 1944 Sept, 1077  
in lymphogranuloma venereum, 1945  
May, 682  
in meningitis, 1945 Sept, 1264  
in nonhemolytic streptococcus subacute  
bacterial endocarditis, 1945 Sept,  
1129  
in pneumococcal meningitis, 1945 May,  
585  
in pneumonia, 1944 Sept, 1074, 1945  
May, 580, 582  
in postabortal and puerperal sepsis,  
1944 July, 828, 835  
in primary atypical pneumonia, 1944  
Sept, 1078  
in puerperal sepsis, 1945 Nov, 1486,  
1489, 1490, 1491, 1537  
in staphylococcal infections, 1944 Sept,  
1029  
sepsis, 1944 July, 860  
in subacute bacterial endocarditis, 1944  
Sept, 1133, 1945 May, 583  
in syphilis in pregnancy, 1945 Nov,  
1468  
in urinary tract infections, 1945 May,  
574, 578

- Penicillin inhalant, 1945 July, 916  
 in bronchiectasis 1945 Sept., 1287  
 methods of administration and dosage,  
 1945 July 909  
 snuff, 1945 July, 916  
 toxic reactions, 1944 Sept., 1040  
 versus sulfonamide therapy, 1945 May  
 579  
 Pentothal narcosynthesis in war neuroses  
 1945 May, 737  
 Peptic ulcer, benign and malignant differ-  
 tiation, 1945 March 495  
 chronic appendicitis simulating 1945  
 May 629  
 diagnosis, 1945 March 489  
 diet in fundamental importance in  
 Army hospital 1945 May, 706  
 differential diagnosis, 1945 May 624  
 dyspepsia in 1944 July, 895 897  
 gastric acidity control of 1944 Sept.,  
 1165  
 gastric catarrh with 1945 May  
 628  
 gastroscopy in, 1945 March 499  
 hemorrhage in, 1943 Nov., 1578  
 1944 March, 414  
 prompt and frequent feeding in  
 1944 Nov., 1351  
 hormonal influences 1944 March  
 411, Nov., 1349  
 therapy, 1944 Nov 1349  
 in asthenic person 1945 May, 625  
 in hypersthenic person 1945 May  
 626  
 in military personnel 1944 Nov.,  
 1353  
 jejunal transplant into stomach wall  
 1944 Nov., 1350  
 malignant 1944 March 416  
 medical treatment, 1944 March 403  
 perforated 1943 Nov 1575  
 psychic factor 1944 March 404  
 pyloric stenosis in 1944 March 415  
 recurrent, therapeutic control 1945  
 Sept., 1162  
 roentgen diagnosis 1945 March 493  
 sodium alkyl sulfate in, 1944 Nov  
 1350 1945 March 426  
 uncomplicated, treatment 1944 Sept.,  
 1164  
 vitamin U" therapy 1945 May, 709  
 with atypical symptoms, 1945 May  
 625  
 Iercomorph liver oil 1943 March 354  
 in rickets, 1943 March 368  
 Perforations, gastrointestinal diagnosis,  
 1943 Nov 1470  
 of eardrum 1944 March 334  
 of peptic ulcer 1943 Nov., 1575  
 Periarthritis nodosa 1944 May 735  
 1945 Jan., 139  
 eosinophilia in 1944 July 918  
 Periarthritis of shoulder, physical therapy  
 in, 1943 July 917, 1012  
 Pericardial effusion in children 1945  
 July, 871  
 Pericarditis acute electrocardiograms in,  
 1945 May 603  
 chronic constrictive, x ray signs, 1944  
 Nov., 1343  
 electrocardiograms in 1945 May,  
 604 609  
 Perimetritis puerperal, 1945 Nov., 1490  
 Periodontoclasia, teeth and 1943 March,  
 548  
 Peripheral arterial occlusion 1943 Nov  
 1546  
 nerve injuries, diagnosis and surgical  
 treatment, 1945 Jan 9  
 physical therapy in, 1943 July, 917,  
 1097  
 vascular diseases, physical medicine in  
 1943 July, 951  
 in aged 1943 July 1013  
 ulcers of extremities due to ty-  
 rothricin in, 1944 July, 849  
 venous thrombosis 1943 Nov., 1548  
 Peritoneal syndrome in nephrosis 1945  
 July 876  
 Peritoneoscopy in liver disorders, 1945  
 March 369  
 Peritonitis, pelvic puerperal 1945 Nov.,  
 1490  
 pneumococcal, sulfamerazine in 1943  
 Nov., 1454  
 Pernicious anemia, 1943 March 467 477  
 1944 Jan., 214 1945 Jan., 229  
 clinical types, 1945 Jan., 230  
 liver therapy 1944 Jan 227, March,  
 374 1945 Jan., 242  
 nervous symptoms, treatment, 1944  
 March 446  
 posterolateral sclerosis in manage-  
 ment, 1945 Jan., 245  
 Peroneal nerve injuries, 1945 Jan., 20  
 Personality 1945 Nov., 1508  
 compulsive-obsessive, 1944 May, 545  
 cycloid, 1944 May 541  
 defined 1944 May 537  
 development 1944 May 531  
 distorted growths 1944 May, 538  
 hysteroid 1944 May 544  
 neurasthenoid, 1944 May 546  
 patterns, 1945 May 746  
 schizoid 1944 May 539  
 structure accident proneness and 1944  
 May 657  
 and deviation in ulcerative colitis,  
 1944 May 595  
 Pertussis See Whooping cough  
 immunization 1945 Sept., 1242  
 Pes cavus 1943 July 1135  
 valgoplanus, 1943 July 1133  
 Pessaries in dysmenorrhea 1943 Jan., 114

- Pessaries in nonreplaceable uterus, 1943 Jan, 114  
 in prolapse of uterus, 1943 Jan, 11, 115  
 in retrodisplacement of uterus, 1943 Jan, 11, 109  
 in sterility, 1943 Jan, 113  
 use of, in gynecology, 1943 Jan, 109
- Petechial fever, 1943 May, 775
- Petit mal, 1945 Sept, 1116, 1123
- Phagocytic index in brucellosis, 1943 May, 712
- Pharmacology, recent advances, 1945 March, 417
- Pharyngitis, acute, sulfonamides in, 1944 July, 799
- Phenobarbital in convulsive disorders, 1944 March, 441  
 in epilepsy, 1945 Sept, 1120
- Phenolsulfonphthalein test of renal function, 1943 Sept, 1268
- Phenytoin sodium in epilepsy, 1945 Sept, 1121
- Pheochromocytoma of adrenal medulla, 1945 July, 1016
- Phlebitis, acute, anesthetization of lumbar ganglia in, 1943 July, 990
- Phlebotomus fever, postwar problem of, 1945 July, 901
- Phlegmasia alba dolens, 1945 Nov, 1492
- Phonation, mechanism of, 1944 Nov, 1333
- Phosphorus as nutrient, 1943 March, 283  
 dietary requirements, 1943 March, 298  
 in pregnancy, 1943 March, 538  
 radio-active, in chronic myelocytic leukemia, 1944 Jan, 195, Nov, 1384
- Phrenology, 1944 March, 452
- Phrynoderma, 1943 March, 356
- Phthalylsulfathiazole See *Sulfathalidine*
- Physical fitness testing of rheumatic fever patients, 1945 May, 719  
 rehabilitation, in Army Air Forces, 1945 May, 717  
 therapy, calcium metabolism and, relationships, 1943 July, 1178  
 following suture of nerves, 1943 July, 1091  
 in after-treatment of amputations, 1943 July, 1109  
 in arthritis, 1945 May, 790  
 in backache, 1943 July, 1057  
 in cerebral palsy, 1945 May, 792, 819  
 in dermatology, 1945 Sept, 1111  
 in fibrositis, 1943 July, 903  
 in hospital organization, place of, 1945 May, 816  
 in orthopedics, 1943 July, 913  
 in peripheral nerve injuries, 1943 July, 1097  
 in poliomyelitis, 1943 July, 883, 915 1945 May, 791  
 in radicular pain, 1943 July, 994  
 in rehabilitation, 1945 May, 786
- Physical therapy in relation to geriatrics, 1943 July, 1007  
 in rheumatoid arthritis, 1944 March, 313  
 in scoliosis, 1943 July, 1025  
 in thrombo-angitis obliterans, 1945 May, 790  
 in tuberculosis, 1945 May, 792  
 in vascular disease, 1943 July, 951  
 in war injuries of spine and spinal cord, 1943 July, 1077  
 military, symposium on, 1943 July, 1024  
 preventive, 1945 May, 788  
 symposium on, 1943 July, 883  
 training, of rheumatic fever patients 1945 May, 768
- Pitocin, 1943 Jan, 29, 1944 Sept, 1267
- Pitressin, 1944 Sept, 1267  
 clinical uses, 1943 Jan, 29
- Pituitary adenoma, 1944 March, 475  
 anterior lobe, disturbances, real vs supposed, 1945 July, 1010  
 basophilism, 1944 March, 477  
 cachexia, 1944 March, 474  
 dwarfism, 1944 March, 476  
 extract, whole posterior, 1944 Sept., 1267  
 gland, anterior, diseases of, 1944 March, 474  
 physiology, 1944 Sept, 1234  
 disease, hypoglycemic crises in, 1943 Nov, 1623  
 posterior, diseases of, 1944 March, 478  
 physiology, 1944 Sept, 1235  
 hormones, 1943 Jan, 27, 1944 Sept, 1234  
 clinical uses, 1944 Sept, 1251, 1266  
 myxedema, 1944 Nov, 1386  
 posterior lobe, disturbances, real vs supposed, 1945 July, 1009
- Placenta accreta, 1943 Nov, 1609  
 circumvallate, 1945 July, 855  
 hormones, 1944 Sept, 1240  
 praevia, 1943 Nov, 1604, 1945 July, 855, 857  
 premature separation, 1943 Nov, 1607, 1945 July, 855, 857  
 retained, 1943 Nov, 1608
- Plague, 1943 May, 745, Nov, 1489  
 as war and post-war problem, 1943 May, 746, 1945 July, 901  
 bubonic, 1943 May, 753  
 clinical features and diagnosis, 1943 May, 752  
 pneumonic, 1943 May, 753, 755  
 prophylaxis, 1943 May, 762, Nov, 1489  
 septicemic, 1943 May, 753, 755  
 ylvatic, 1943 May, 749  
 treatment, 1943 May, 760

- Plantar calluses and corns, 1943 July 1135, 1142  
 warts, 1943 July, 1143  
 Plasma administration in burns, 1943 Sept., 1231 1235  
 in gastrointestinal hemorrhage 1943 Nov., 1579  
 in hemorrhage, 1943 Nov., 1544  
 application in medicine 1943 Jan., 157  
 bovine, for human use, 1945 March 433  
 composition, 1943 Jan., 177  
 dried, 1943 Jan., 184  
 fractionation, products and uses, 1943 Sept., 1086  
 frozen 1943 Jan., 183  
 heterologous, uses, 1945 Sept., 1091  
 in shock, 1945 Sept., 1082  
 liquid 1943 Jan., 181  
 proteins, 1943 March 305  
 reactions following use 1945 Sept. 1088  
 transfusions, 1943 March, 310  
 uses and indications, 1945 Sept., 1079  
 Plasmochin in malaria, 1943 Nov., 1480  
 Plasmodia, 1943 May, 618 Sept 1417  
 1944 Nov., 1438  
 Laboratory identification 1944 Nov., 1455 1458  
 Plasmoquin in malaria, 1943 May, 628  
 Platelet count 1944 Jan., 156  
 Plethora abdominalis, 1944 May 722  
 Pleura malignant tumors effusions due to 1945 March, 509, 512  
 Pleural effusions, diagnosis and treatment, 1945 March 502  
 emergency aspects 1945 July 846  
 Pleurisy emergency aspects, 1945 July 846  
 Pneumococcal infections of eye sulfonamides in 1944 July 794  
 sulfonamides in 1943 Nov 1452  
 meningitis, 1943 Nov., 1504, 1945 Sept., 1267  
 sulfonamides in, 1944 July 870 872  
 Pneumonectomy in tuberculosis 1945 March, 451  
 Pneumonia, 1943 Sept., 1291 1944 Sept., 1067  
 atypical primary etiology unknown 1943 May, 670 Sept 1294  
 as seen in tropics, 1944 Nov., 1490  
 sulfonamides and penicillin in 1944 Sept., 1078  
 common forms, differential diagnosis, 1943 Sept., 1300  
 emergency aspects 1945 July 840  
 Friedländer's bacillus, 1943 Sept., 1292  
 hemolytic streptococcus, 1943 Sept., 1292  
 hospital care value, 1944 July 808  
 in armed forces in S Pacific 1944 Nov., 1422  
 Pneumonia, in childhood, 1943 Nov., 1526 1945 July, 868  
 sulfonamides in 1944 July, 887  
 laboratory examinations, 1943 Sept. 1295  
 management, common problems 1944 July 804  
 nonspecific therapy, 1943 Sept., 1305  
 penicillin in 1944 Sept., 1074 1945 May 580, 582  
 pneumococcal, 1943 Sept. 1291  
 arotherapy and chemotherapy 1943 Sept., 1299 1302 1452  
 sulfamerazine in 1945 March 294  
 postoperative prevention breathing exercises for 1945 May, 789  
 puerperal, 1945 Nov., 1537  
 roentgenography in value, 1944 July 807  
 staphylococcal, 1943 Sept. 1293  
 with bacteremia, penicillin in 1944 Sept 1031  
 sulfadiazine in method and results in 533 cases, 1944 Jan., 267  
 sulfonamides in 1943 Sept., 1299  
 1944 July 805, 808 Sept., 1068  
 1943 Sept., 1310  
 treatment, recent advances, 1943 Sept., 1291 1299  
 specific, present day 1944 Sept., 1067  
 virus, 1943 Sept., 1293  
 Pneumothorax, spontaneous emergency aspects, 1945 July 844  
 Polson Ivy extract, 1945 Sept., 1105  
 Poisons, ingestion by children management 1945 July 884  
 Pollomyelitis, 1943 Nov 1530  
 acute stage, treatment 1943 Sept., 1339  
 chronic, 1944 March 449  
 Kenny treatment, 1943 July 883  
 evaluation 1943 Sept., 1345 1348  
 neostigmine in, 1945 March 423  
 nonparalytic, 1943 Sept., 1339  
 physical medicine in, 1945 May, 791  
 physiotherapy 1943 July 883, 915  
 respirator in 1943 Sept., 1350  
 with bulbar paralysis 1943 Sept., 1351  
 with spinal type of respiratory paralysis, 1943 Sept., 1349  
 with temporary paralysis of left leg 1943 Sept., 1344  
 Polka fever 1943 May 808  
 Polyarthrits, acute migratory in large station hospital 1944 Jan., 124  
 Polymenorrhea 1944 Sept., 1218 1220  
 hormone therapy 1944 Sept., 1227  
 Polyneuritis of nutritional deficiency 1943 March 419  
 Polys, aural 1944 March 336  
 Polyuria in hyperparathyroidism, 1945 March 395

- Portal vein, thrombosis of, 1944 May, 733  
 Postabortal infections, penicillin in, 1944 July, 835  
   sulfonamides in, 1944 July, 827  
 Posterolateral sclerosis in nutritional deficiency, 1943 March, 425  
 Postnasal discharge with hyperemic lymphoid tissue, radium treatment, 1944 Nov, 1331  
 Postpartum hemorrhage, 1943 Nov, 1610, 1945 July, 855, 858, Nov, 1537  
   infections, 1945 July, 859  
   psychosis, 1945 Nov, 1517  
 Postural abnormalities, physical therapy, 1943 July, 1001  
   arthralgia, 1945 Sept, 1271  
   exercises in occlusive arterial diseases, 1943 July, 962  
   joint strain, 1943 Sept, 1311  
   strain, backache due to, 1943 July, 1064  
 Posture, malalignment of feet and, 1943 July, 944  
   physical principles in, 1943 July, 937  
   poor, as cause and effect of disease, 1943 July, 946  
   physical therapy in, 1943 July, 919  
 Potassium chloride in cataplexy, 1945 March, 422  
   in myasthenia gravis, 1945 Jan, 135  
   permanganate soaks in epidermophytosis, 1944 Nov, 1533  
   salts, effects on electrocardiogram, 1945 May, 613  
   sulfocyanate in hypertension, 1943 Sept, 1268  
   thiocyanate in hypertension, 1944 Sept, 1146  
 Pourodign, 1945 March, 423  
 Powders, dermatologic, 1945 Sept, 1097  
 P-R interval, prolongation, in rheumatic fever, 1944 Jan, 61  
 Precordial pain, differential diagnosis, 1945 March, 513  
 Pre-eclampsia, 1945 March, 538, 541, July 850, Nov, 1436, 1440  
 Pre-eclamptic toxemia, prevention, 1943 Nov, 1597  
   treatment, 1943 Nov, 1598  
 Pregnancy, anemia of, 1944 March, 377  
   blood transfusions in, 1944 Jan, 250, 264  
   dermoid tumor of ovary and, in young girl, 1943 Jan, 23  
   diabetes and, 1945 Nov, 1477  
   heart disease and, management, 1945 Nov, 1449  
   early, hemorrhage of, 1945 July, 853  
   ectopic, 1945 Nov, 1601, 1603  
   ruptured, 1945 July, 854, 856  
   hemorrhage of, 1943 Nov, 1601  
   late, hemorrhage of, 1945 July, 855  
 Pregnancy, macrocytic anemia of, 1945 Jan, 247  
   mitral disease and, 1944 Jan., 51  
   nutrition in, 1943 March, 537, 574  
   pernicious vomiting of, 1945 July, 848  
   Rh typing in 1945 Nov, 1546  
   psychiatric aspects, 1945 Nov, 1514  
   syphilis and, management, 1945 Nov., 1463  
   tests for, 1945 Nov, 1553  
   toxemias of, 1943 Nov., 1596, 1945 July, 848, Nov, 1945  
   treatment, 1945 Nov, 1440  
   tuberculosis and, 1945 Nov, 1454  
   vaccination during, as prophylaxis against puerperal infections, 1945 Nov, 1495  
 Pregnant mare serum, 1944 Sept, 1250  
 Pregnenolone, 1944 Sept, 1257  
   in dysmenorrhea, 1945 Nov., 1403  
   in threatened abortion, 1945 Nov, 1405  
 Premarital advice, 1943 Jan, 14, 1945 Nov, 1349  
 Premature infant, 1943 Nov, 1520  
 Premenstrual tension, 1943 Jan, 38, Sept, 1381  
 Prepuce, redundant, 1945 July, 877  
 Pressure dressings in burns, 1943 Sept, 1237  
   exercises in after-treatment of amputations, 1943 July, 1115  
 Preverbal stage, psychosomatic conditions in, 1944 May, 556  
 Procaine hydrochloride for local anesthesia, 1945 March, 419  
 Proctitis in lymphogranuloma venereum, 1945 May, 673  
 Progesterone, 1943 Jan, 29, 31 1944 Sept, 1256  
   in amenorrhea, 1943 Sept, 1375, 1945 Nov, 1381, 1400  
   in dysmenorrhea, 1943 Jan, 35, 1945 Nov, 1402  
   in functional uterine bleeding, 1943 Sept, 1378, 1379, 1945 Nov, 1385, 1398  
   in hypermenorrhea, 1944 Sept, 1223  
   in hypoovarianism, 1944 March, 481  
   in threatened abortion, 1945 Nov, 1405  
   therapeutic test, 1944 Sept, 1247  
   therapy in menstrual disorders, 1945 Jan, 263  
   to stimulate ovulation, 1944 Sept, 1226  
 Progestins, clinical uses, 1944 Sept, 1256  
 Progestogens, 1944 Sept, 1256  
 Progynon-B to stimulate ovulation, 1944 Sept, 1225  
 Prolactin, 1943 Jan, 28  
   in functional uterine bleeding, 1945 Nov, 1399  
 Prolapse of uterus, pessaries in, 1943, Jan, 11, 115

- Proluton in polymenorrhea 1944 Sept., 1227  
     to stimulate ovulation 1944 Sept., 1226  
 Promin in tuberculosis, 1945 March 447, 448 July 919  
 Promizole in tuberculosis, 1945 July 921  
 Prontylin. See *Sulfanilamide*  
 Propadrine in asthma in children, 1945 July 867  
     in coryza, 1945 March 420  
 Propionate propionic acid ointment in dermatophytosis, 1945 March, 326  
 Prostate gland, carcinoma estrogen therapy, 1945 March 435  
     physiology 1944 Sept., 1239  
 Prostatic enlargement, acute urinary retention due to, 1943 Nov., 1563  
 Prostatitis, gonorrheal 1944 March 514  
 Prostheses after amputation, 1943 July 1118  
 Prostinine in amenorrhea 1945 Nov., 1382  
     in myasthenia gravis, 1945 Jan., 131  
     diagnostic test, 1945 Jan., 128  
     laryngis, 1944 Nov., 1333  
 Protamine zinc insulin 1944 Sept., 1060 1272  
 Protein alimentation oral, 1943 March, 308  
     parenteral 1943 March, 308  
     deficiency clinical types 1943 March 306  
     dietary requirements, 1943 March, 296  
     hydrolyzed See *Amigen*  
     metabolism, 1943 March 303  
     serum in liver disease, 1945 July 979  
 Prothrombin deficiency plasma in 1945 Sept 1085  
     determinations, 1943 March 372, 505  
     time in dicoumarol therapy 1945 July 930  
     in liver disease, 1945 July, 978  
 Protrusion of intervertebral disk, 1945 Jan., 111  
 Pruritus vulvae 1943 Jan., 5 1945 Nov., 1366  
 Pseudohermaphroditism 1945 Nov., 1388  
 Pseudomonas aeruginosa infections of eye sulfonamides in 1944 July 794  
 Psychasthenia 1944 May 672  
 Psyche 1944 May 531  
     and soma, 1944 May 554  
 Psychiatric disorders in combat crews overseas 1945 May 729  
     in returnees 1945 May 733  
     problems in gynecology and obstetrics 1945 Nov., 1508  
 Psychiatrist, function of in court, 1945 Jan., 211  
 Psychiatry practical 1945 Sept 1231  
 Psychic factor in peptic ulcer, 1944 March 404  
 Psychoanalysis, 1944 March, 452  
 Psychogenic states, arthralgia in 1943 Sept., 1320  
 Psychological readjustment in rehabilitation program Army Air Forces, 1945 May 723  
 Psychomotor seizure 1945 Sept., 1116 1123  
 Psychoneurosis, anoxia as cause of 1944 May 709  
     transitory in soldiers, reconditioning in 1945 May 751  
     traumatic, 1944 May, 663 666  
 Psychopathology basic principles, 1945 Nov 1508  
 Psychoses convulsive shock therapy 1945 Sept., 1232  
     criminal responsibility in 1945 Jan., 195  
     electric convulsive therapy 1943 July 1019 1945 Jan., 163  
     insulin shock therapy 1945 Sept. 1231  
     pellagrous, 1943 March 391 431  
     postpartum 1945 Nov 1517  
     prefrontal lobotomy in, 1945 Sept. 1232  
     psychotherapy in 1945 Sept., 1231  
     war barbiturates in 1945 March 418  
     with insomnia, electroshock and insulin shock therapy 1945 Jan., 192  
 Psychosomatic aspects of medical practice in wartime 1943 Nov 1633  
     of rehabilitation, 1945 May 740  
     disorders, gastrointestinal 1944 May, 557 561 Sept., 1154, Nov, 1355  
     interviewing patients with, technic, 1944 Sept., 1210  
     factors in disorders of circulatory system 1944 May, 565  
     in stuttering, 1944 May, 615  
     in ulcerative colitis, 1944 May, 593  
     in young children's colds 1944 May 603  
 medicine, clinical description 1944 May 525 559  
     concepts of 1944 May 555  
     methods of 1944 May 558  
     principles of 1944 May 553, 1945 May 742  
     symposium on 1944 May 525  
     states, in combat crews 1945 May 732  
     in returned soldiers, 1945 May, 736  
 Psychotherapy essentials of 1944 May 548  
     for practitioner 1944 May 546  
     in cardiospasm 1944 May 591  
     in certain circulatory disorders 1944 May, 573  
     in cycloidism 1944 May 543  
     in fatigue and exhaustion states 1945 May 781



- Psychotherapy in hypertension, 1943 Sept., 1273  
 in hysteroid personality, 1944 May, 545  
 in insomnia, 1945 Jan., 186  
 in psychoses, 1945 Sept., 1231  
 in recurrent peptic ulcer, 1945 Sept., 1162  
 in schizoidism, 1944 May, 541  
 in ulcerative colitis, 1944 May, 598  
 in war neuroses, 1945 May, 737  
 steps in, 1945 Nov., 1513
- Psychotic-like states in combat crews, 1945 May, 732  
 in returned soldiers, 1945 May, 736
- Puerperal infections, 1945 Nov., 1537  
 prevention and treatment, 1945 Nov., 1483  
 prophylaxis, vaccination during pregnancy as, 1945 Nov., 1495
- sepsis, 1943 Nov., 1611, 1945 July, 859  
 antiseptic solutions, prophylactic, 1944 July, 830  
 penicillin in, 1944 July, 828, 835  
 sulfonamides in, 1944 July, 827
- Pulmonary See also *Lungs*  
 complications, postoperative in asthmatic patient, 1944 July, 995  
 embolism, 1943 Nov., 1550  
 electrocardiograms in, 1945 May, 605  
 emergency aspects, 1945 July, 839  
 prevention, exercises for, 1945 May, 789  
 emphysema, obstructive, 1944 March, 356  
 stenosis, 1944 Jan., 99  
 thrombosis, 1943 Nov., 1550
- Pulsus alternans, electrocardiograms in, 1945 May, 617
- Purpura haemorrhagica, 1944 Jan., 163  
 Henoch's, 1945 July, 880  
 thrombocytopenic, 1944 Jan., 153  
 essential, 1944 Jan., 163  
 symptomatic, 1944 Jan., 179
- Pyelitis in infants, 1943 Nov., 1526  
 treatment, 1944 Sept., 1183
- Pyelonephritis, 1943 Jan., 246, Nov., 1559, 1944 Sept., 1183  
 acute diffuse, in children, 1945 July, 875  
 atrophic, 1945 March, 541  
 in hyperparathyroidism, 1945 March, 394
- Pyemia, puerperal, 1945 Nov., 1492
- Pyloric stenosis in infants, 1943 Nov., 1524  
 in peptic ulcer, 1944 March, 414
- Pylorospasm in infants, 1943 Nov., 1524
- Pyoderma, extensive, sulfonamides in, 1944 July, 846  
 gangraenous, sulfonamides in, 1944 July, 846
- Pyorrhea, dentition and, 1943 March, 548
- Pyramidal tract signs, pathologic, 1945 Jan., 45
- Pyrotherapy See *Fever therapy*
- QUICK prothrombin time test in dicoumarol therapy, 1945 July, 930
- Quinidine, effects on electrocardiogram, 1945 May, 611  
 in auricular fibrillation, 1945 Jan., 217  
 in auricular flutter, 1945 Jan., 223  
 in paroxysmal tachycardia, 1943 Nov., 1539, 1945 Jan., 226  
 parenteral use, 1944 Nov., 1345  
 uses and abuses, 1945 Jan., 215
- Quinine in malaria, 1943 May, 626, 628, Nov., 1479  
 test for myasthenia gravis, 1945 Jan., 129, March, 422
- RABIES, 1943 Nov., 1514  
 immunization, 1945 Sept., 1243  
 some practical questions and answers, 1944 Nov., 1406
- Racephedrine hydrochloride, 1945 March, 420
- Radial nerve injuries, 1945 Jan., 10
- Radiation sickness, vitamin therapy, 1943 March, 578
- Radicular pain, 1943 July, 994  
 physical therapy for, 1943 July, 1001
- Radiculoneuritis, acute infectious, 1945 Jan., 1
- Radio-active phosphorus in chronic myelocytic leukemia, 1944 Jan., 195
- Radium treatment of deafness in childhood, 1944 March, 337  
 of functional uterine bleeding, 1945 Nov., 1385  
 of nasopharyngeal lymphoid masses, 1944 Nov., 1332
- Railroad spine, 1944 May, 664
- Rash in dengue fever, 1943 May, 815  
 in Rocky Mountain spotted fever, 1943 May, 727
- Rat tests for pregnancy, 1945 Nov., 1554
- Rations, military, 1943 March, 581
- Raynaud's disease, diagnosis, 1945 July, 942
- Reaction types, mental, 1945 Nov., 1510
- Reconditioning of malaria patient, 1945 May, 760  
 of transitorily maladjusted soldiers, 1945 May, 751  
 program, Army, 1945 May, 788  
 Army Air Forces, 1945 May, 717
- Rectal swabs in shigellosis, 1943 May, 694
- Rectosigmoid, carcinoma, errors in diagnosis, 1944 Jan., 278

- Rectum carcinoma, errors in diagnosis  
1944 Jan., 278  
stricture, in lymphogranuloma venereum  
1945 May 673, 674 683
- Reduction diet, 1943 March, 345 346
- Reflexes in neurasthenia, 1944 May 677
- Refrigeration in impaired arterial circulation, 1943 July 954  
use of in military medicine, 1943 July, 1166
- Rehabilitation after amputations, 1943 July, 1121  
Federal, State and Industry's interest in  
1945 May, 817  
in Army Air Forces, 1945 May, 715  
in civilian medical practice, 1945 May 807  
nutrition in 1945 May 794  
of malaria patient, 1945 May 760  
of rheumatic fever patients, 1945 May 765  
of transitorily maladjusted soldiers, 1945 May 751  
physical medicine in 1945 May 786  
postwar possibilities, 1945 May 725  
psychosomatic aspects 1945 May, 740  
symposium on, 1945 May 714
- Rekoss disk, 1944 May 745
- Relapsing fever, 1943 May 734, Nov., 1485  
louse borne, 1943 May 737 Nov., 1486  
tick borne 1943 May, 738 Nov., 1485  
treatment, 1943 May, 743
- Renal See also Kidney  
colic, 1943 Nov 1569  
retinitis 1944 May, 749
- Respirator in poliomyelitis, 1943 Sept., 1350
- Respiratory data laboratory, in health and disease, 1945 Sept., 1322  
diseases in aged physical therapy in  
1943 July 1016  
in infants 1943 Nov., 1525  
industrial disability and 1944 Nov., 1293  
infectiousness of air and relationship, 1944 Nov., 1300  
infections, epidemiology and bacteriology among armed forces of South Pacific, 1944 Nov., 1418  
upper acute, sulfonamides in 1944 July 798  
tract nonsurgical emergencies, in childhood, 1945 July 864
- Rest in congestive heart failure, 1944 March 382  
in functional disorders of digestive tract, 1944 March 426
- Retina, central artery occlusion of, 1943 Nov., 1552
- Retinitis, 1944 May, 748  
diabetic, 1944 May, 749  
hemorrhagic, vitamin therapy 1943 March 559  
proliferans, 1944 May, 749  
renal 1944 May, 749  
septic, 1944 May 750
- Retroduplacements of uterus, pessaries in, 1943 Jan., 11, 109
- Retrogasserian neurotomy, classical for facial pain, 1945 Jan., 80  
posterior, for facial pain, 1945 Jan., 83
- Returnees, psychiatric disorders in, 1945 May, 733
- Rb factor, 1944 Jan., 232, 254 1945 Nov., 1546  
and erythroblastosis foetalis 1944 Jan., 240 258  
blood transfusion and 1945 Sept., 1076  
in obstetrics, 1944 Jan., 240 254  
in transfusion reactions, 1944 Jan., 236 250 256 March 379  
testing for 1944 Jan., 250 1945 Nov., 1547
- Rheumatic conditions, common treatment 1943 Sept., 1309  
etiology, environmental factors, 1945 May 566  
fever 1943 Sept., 1280  
convalescence, physical fitness testing and physical training in 1945 May 719  
in Army Air Forces, convalescent care 1945 May 765  
penicillin failure in, 1945 May 580  
pleural effusion in 1945 March 508  
P R interval prolongation in significance 1944 Jan., 61  
present-day concepts, 1945 July 923  
recent advances, 1944 Nov 1338  
sodium salicylate in 1945 March 425  
sulfadiazine in, prophylactic, 1945 March 425  
sulfonamides in prophylactic, 1944 July, 838 889  
survey of in large station hospital 1944 Jan., 124
- heart disease 1943 Sept., 1279 1944 Jan., 127 Sept., 1129 1945 Nov., 1451
- Infection, recurrence of 1943 Sept., 1282
- valvular disease chronic, 1943 Sept., 1282
- Rheumatismus febrilis exanthematicus 1943 May, 803
- Rheumatoid arthritis 1943 Sept., 1332 1945 Sept., 1277  
advances in study and treatment. 1944 March 309

- Rheumatoid arthritis, etiology, environmental factors, 1945 May, 566  
fever therapy, 1943 July, 1123  
gold salts in, 1944 March, 316  
histamine and mecholyl iontophoresis in, 1944 March, 319  
neostigmine in, 1945 March, 423  
physical therapy, 1943 July, 1008, 1944 March, 313  
vitamin D in, 1944 March, 314  
spondylitis, 1943 Sept., 1338
- Rhinitis, acute, sulfonamides in, local use, 1944 July, 802  
gonadal relationships, 1944 Nov., 1329
- Riboflavin deficiency, 1943 March, 399  
diet in, 1945 May, 803  
early, 1943 March, 495  
mouth lesions, 1943 March, 401, 550  
pathology, 1943 March, 514  
dietary requirements, 1943 March, 293  
dosages, 1945 Sept., 1302  
enzyme relationships, 1943 March, 280  
in deficiency diseases, 1943 March, 274
- Rickets, 1943 March, 361  
early, 1943 March, 495  
pathology, 1943 March, 516  
physical therapy in, 1943 July, 915
- Rickettsia prowazeki, 1943 May, 777  
rickettsii, 1943 May, 723
- Ring pessaries, 1943 Jan., 111, 116, 118
- Ringworm, 1945 March, 323  
of hands and feet in soldiers in tropics, 1944 Nov., 1532
- Risser jacket in scoliosis, 1943 July, 1035
- Rocky Mountain spotted fever, 1943 May, 722, 1944 May, 752
- Roentgen appearance of skeletal changes, in hyperparathyroidism, 1945 July, 1028  
diagnosis, adenoid, bronch sinusitis, 1944 Sept., 1093  
bronchiolitis, acute, in infants, 1944 Sept., 1101  
carcinoma of stomach, 1945 March, 495  
early, 1944 Nov., 1352  
cardiovascular disease, 1944 Nov., 1342  
coccidioidomycosis, 1943 May, 803  
in endocrinology, 1944 Sept., 1247  
peptic ulcer, 1945 March, 493  
placenta praevia, 1943 Nov., 1605  
rickets, 1943 March, 365  
scurvy, 1943 March, 444  
sprue, 1943 March, 460  
tuberculosis, rapid screening methods, 1945 March, 544  
examination in pneumonia, value, 1944 July, 807  
treatment, amenorrhea, 1945 Nov., 1382  
chronic myelocytic leukemia, 1944 Jan., 194, 196, Nov., 1383
- Roentgen treatment, Hodgkin's disease, 1944 Jan., 211  
leukemia, 1943 Jan., 255  
peripheral vascular disease, 1943 July, 989  
sinusitis, 1944 Nov., 1  
subacute leukemia, 1944 Jan., 190
- Roentgenogram, pelvic tilt, 1943 July, 1032
- Roentgenoscopy, protection in, 1945 July, 1036
- Roger's disease, 1944 Jan., 60
- Rorschach ink-blot tests in stuttering, 1944 May, 623
- Roseola infantum, 1943 Nov., 1527
- Rossolimo sign in pyramidal tract lesions, 1945 Jan., 53
- Rubin test for tubal patency, 1943 Jan., 9, 61
- Russian encephalitis, 1943 Nov., 1513
- SACRO-ILIAC strain, acute, 1943 July, 1066
- Salicylates in rheumatic fever, 1943 Sept., 1281  
heart disease, 1944 Sept., 1130
- Salpingitis, gonorrheal, sulfonamides in, 1944 July, 832
- Salyrgan-theophylline, as diuretic, 1945 March, 424
- Sanders oscillating bed, 1943 July, 985
- Sandfly fever, postwar problem of, 1945 July, 901
- Sandoz, 1945 March, 424
- Scalp, dermatophytosis of, 1945 March, 323
- Scarlatina mitis, exanthematis arthrosia, 1943 May, 808
- Scarlet fever, 1943 May, 661, Nov., 1528  
immunization, 1945 Sept., 1247  
sulfonamides in, 1944 July, 888
- Schick test in diphtheria, 1943 May, 656, 659
- Schistosoma haematobium, 1943 May, 848  
infection with, 1943 May, 853  
japonicum, 1943 May, 848  
infection with, 1943 May, 856  
mansoni, 1943 May, 848  
infection with, 1943 May, 854
- Schistosomiasis, 1943 May, 848, Nov., 1494  
asiatic, 1943 May, 856  
intestinal, 1943 May, 854  
postwar problem of, 1945 July, 907  
urinary, 1943 May, 853
- Schizoid personality, 1944 May, 539, 540
- Schizophrenia, 1944 May, 533, 667, 1945 Jan., 150  
insulin shock therapy, 1945 Sept., 1231  
modern concept of, 1945 Jan., 147
- Schizotrypanosomiasis, 1943 May, 822
- Schuster's test, 1944 July, 937

- Sciatic nerve injuries, 1945 Jan., 20  
 Sciatica, 1945 May, 569  
 Sclerosis, combined, in aged physical therapy in 1943 July, 1016  
 posterolateral, in nutritional deficiency, 1943 March, 425  
 management in pernicious anemia, 1945 Jan., 245  
 Scoliosis, physical therapy in, 1943 July, 919 1002  
 structural, treatment 1943 July 1025  
 Scopolamine in parkinsonism 1944 March, 443  
 Screening in malaria control 1943 May 629  
 Scrotum, lymph, 1943 May, 864  
 Scrub typhus, 1944 Nov., 1464  
 Scurvy 1943 March 441  
 diet in, 1945 May, 803  
 pathology 1943 March 515  
 vitamin therapy, 1943 March 274  
 wound healing and 1943 March 561  
 Seasickness, benzedrine sulfate in therapeutic evaluation in 100 cases, 1943 Nov., 1652  
 Seborrhea in riboflavin deficiency 1943 March, 402 405  
 Keratosis 1944 July 969  
 Secretions, internal decreased as cause of deficiency states, 1943 March 525  
 Sedatives in bronchial asthma 1944 March 344 351  
 in convalescence 1945 Sept., 1213  
 in psychosomatic disorders abuse of 1945 May 748  
 Sedimentation rate of erythrocytes, clinical significance 1945 July 937  
 Semen examination, 1943 Jan., 60  
 Sensory disorders, chronic, management 1944 March, 437  
 simulated 1944 July 937  
 Sepsis, postahortial chemotherapy in, 1944 July 827  
 puerperal, 1943 Nov., 1611 1945 July 859  
 chemotherapy in 1944 July 827  
 staphylococcal, penicillin 1944 July 860  
 Septicemia, puerperal 1945 Nov., 1491  
 Serological tests for arthropod borne virus encephalitis, 1943 May 642  
 Serum albumin human 1945 Sept., 1086  
 blood See *Blood serum*  
 uses and indications 1945 Sept., 1079  
 bovine despicated 1945 Sept., 1091  
 convalescent 1943 Jan 157, 158  
 1945 Sept. 1085  
 dried 1943 Jan 181  
 globulin immune, 1945 Sept., 1087  
 human applications in medicine, 1943 Jan 157  
 composition 1943 Jan., 177  
 Serum hyperimmune, 1945 Sept., 1085  
 liquid, 1943 Jan., 180  
 pooled adult, 1943 Jan., 159  
 reactions, 1943 Sept., 1304  
 therapy in bacillary dysentery, 1943 Sept 1215  
 in brucellosis, 1943 Jan., 265, May 715  
 in meningitis, 1945 Sept., 1263, 1266  
 in meningococcal meningitis, 1943 Sept., 1205, Nov., 1502  
 in plague, 1943 May, 761  
 in pneumococcal meningitis, 1943 Nov., 1505  
 in pneumonia, 1943 Sept., 1303  
 Seven-day fever 1943 May 808  
 Sex factors in neuroses 1943 Nov., 1639  
 glands disturbances 1945 July, 1015  
 Sexual dissatisfaction problem of, 1945 Nov., 1372  
 neurasthenia, 1944 May 678  
 Shark liver oil, 1943 March 354  
 Shell shock, 1944 May 666  
 Shigella dysenteriae, 1943 May, 692  
 Shigellosis, 1943 May, 687 692  
 treatment 1943 May 694  
 Shingles treatment, 1944 March, 442  
 Ship fever 1943 May, 775  
 Shock, blood and blood substitutes in, 1943 Jan., 164 167  
 human serum albumin in 1945 Sept., 1086  
 in burns, 1943 Sept 1230 1233  
 sodium lactate in, 1945 March 438  
 irreversible, prevention, 1943 Sept., 1401  
 physiologic mechanisms with therapeutic implications, 1943 Sept., 1400  
 plasma in 1945 Sept., 1082  
 treatment of psychoses, 1943 July 1019 1945 Jan., 165 Sept., 1231 1232  
 prevention of fractures curare for 1945 March, 423  
 Shoes, faulty and foot disability in Army 1943 July 1136  
 Shorr strain 1945 Nov., 1549  
 Shoulder injuries and infections physical therapy in 1943 July, 917  
 painful 1945 May 569  
 periarthritis physical therapy 1943 July 1012  
 Sickle cell anemia 1944 March 379  
 Siderodromophobia 1944 May 675  
 Sign of the groove in lymphogranuloma venereum 1945 May 668 669  
 Silicosis, aluminum powder in 1945 March 437  
 in interstitial cystitis, 1944 July 1013  
 Simmonds' disease 1944 March 474

- Sinus thrombosis, cavernous, emergency treatment, 1945 July, 894  
 swimming in relation to, 1944 Sept, 1126
- Sinusitis, acute, sulfonamides in, 1944 July, 799  
 treatment, 1944 Sept., 1113  
 chronic, 1944 March, 330  
 sulfonamides in, local use, 1944 July 801, 802  
 colloidal calcium gluconate in, 1944 Nov., 1329  
 desoxyephedronium sulfathiazole in, 1944 Nov., 1328  
 x-ray treatment, 1944 Nov., 1329
- Sippy diet, modified, 1943 Nov., 1581
- Six-day fever, 1943 May, 808
- Skin, abrasions, treatment in diabetes, 1944 July, 980  
 care in convalescence, 1945 Sept., 1215  
 diseases, common, treatment, 1945 Sept., 1095  
 in hospital in tropics, 1944 Nov., 1532  
 sulfonamides in, indications and limitations, 1944 July, 844  
 grafting, in burns, 1943 Sept., 1243  
 lesions, in early nutritional deficiencies, 1943 March, 488  
 in pellagra, 1943 March, 382  
 in vitamin A deficiency, 1943 March, 356  
 test in brucellosis, 1945 March, 354
- Sleep paralysis, 1944 July, 945
- Sleeping sickness, African, 1943 May, 835
- Sleeplessness, 1945 Jan., 178  
 clinical effects, 1945 Jan., 181  
 treatment, 1945 Jan., 184
- Smallpox, 1943 May, 603, 615, Nov., 1528  
 immunization, 1945 Sept., 1247
- Smears, obtaining, in gonorrhea in women, 1943 Jan., 90  
 vaginal, 1944 Sept., 1245  
 for ovarian function and uterine cancer, 1945 Nov., 1548
- Smell, hysteric affections of, 1944 May, 692
- Smith pessary, 1943 Jan., 109, 111
- Smithwick's hypertensive work-up, 1944 Sept., 1135  
 splanchnic resection in malignant hypertension, 1944 Sept., 1135, 1136
- Smoking, recurrent peptic ulcer and, 1945 Sept., 1169
- Snake venom in thrombocytopenic purpura, 1944 Jan., 169
- Snoring, sylnasol for, 1944 Nov., 1331
- Soap Lake treatment of thrombo-angitis obliterans, 1943 July, 952
- Sodium alkyl sulfate in peptic ulcer, 1944 Nov., 1350, 1945 March, 426
- Sodium citrate in lead poisoning, 1945 March, 437
- Lactate in burn shock, 1945 March, 438
- propionate in fungus infections, 1945 March, 438
- salicylate in rheumatic fever, 1945 March, 425
- sulfanilyl sulfanilate in lymphogranuloma venereum, 1945 May, 682
- Soldiers, combat, psychiatric disorders in, 1945 May, 729  
 heart, 1944 May, 569  
 decrease in, in World War II, 1944 May, 560  
 returned from combat, psychiatric disorders in, 1945 May, 733  
 transitorily maladjusted, reconditioning of, 1945 May, 751  
 veteran, psychosomatic disorders in, 1945 May, 740
- Soma and psyche, relation of, 1944 May, 554
- Somatic phase of mental growth, 1944 May, 531
- Sore throat, septic, common source with scarlet fever, 1943 May, 664  
 streptococcal, 1943 Sept., 1202  
 treatment, 1944 Sept., 1114
- Spasmodic torticollis, treatment, 1944 March, 449
- Spastic colitis, 1944 March, 418  
 paralysis, cerebral, physical therapy in, 1943 July, 914
- Speech disorders, simulated, 1944 July, 939  
 hysteric affections of, 1944 May, 692
- Spermatozoa count, 1944 Sept., 1246
- Spiller-Frazier operation for facial pain, 1945 Jan., 80
- Spinal anesthesia, single dose and continuous, for labor and vaginal delivery, 1945 Nov., 1538  
 cord, subacute combined degeneration, in nutritional deficiency, 1943 March, 425  
 war injuries, 1943 July, 1083  
 after-care, 1943 July, 1087  
 muscular atrophy, progressive, 1944 March, 449
- Spine, congenital anomalies, 1943 July, 1070  
 fractures, arthritis in, 1943 Sept., 1332  
 injuries and infections, arthritis in, 1943 July, 919  
 "railroad," 1944 May, 667  
 war injuries, with special reference to physical treatment, 1943 July, 1077, 1079
- Spinous process, fractures, 1943 July, 1080
- Spirillum cholerae asiaticae, 1943 May, 766

- Spirochaeta duttoni*, 1943 May, 736  
*recurrentis* 1943 May 736  
*veneruelensis*, 1943 May, 740  
 Splanchnicectomy in hypertension, 1944 Sept., 1135 1136  
 Spleen, infarction of 1943 Nov 1552  
 Splenectomy in hemolytic anemia, 1945 May, 704  
     in thrombocytopenic purpura, 1944 Jan., 158  
 Splints, arthroplasty, 1943 July, 916  
 Spondylitis brucella, 1945 March, 351  
     physical therapy, 1943 July, 1003  
     rheumatoid, 1943 Sept., 1338  
 Spondylolisthesis, 1943 July, 1070  
     physical therapy in, 1943 July, 920  
 Sporotrichosis, 1945 March, 328  
 Spotted fever, Rocky Mountain, 1943 May, 722  
     typhus, 1943 May, 775  
 Sprains, foot, 1943 July, 1146  
 Sprue, 1943 March, 451  
 Sputum examinations in pneumonia, 1943 Sept., 1295  
 St. Louis type of encephalitis 1943 May 633 Nov., 1509  
 Staining methods for malarial parasites, 1944 Nov., 1458  
 Staphylococcal infections, penicillin in 1944 Sept., 1029  
     sulfamerazine in, 1943 Nov., 1455  
     sulfonamides in 1943 Sept., 1253  
     meningitis, 1943 Nov., 1506, 1945 Sept., 1268  
     pneumonia, 1943 Sept., 1293  
     sepsis, penicillin in, 1944 July, 860  
 Starvation treatment of gastro-intestinal hemorrhage 1943 Nov., 1580  
 Status apoplectic, 1944 May, 722  
     asthmaticus 1944 March, 339  
 Steam inhalations in bronchial asthma 1945 March 458  
 Steatorrhea, pancreatic, pancreatic enzyme in, 1945 March, 429  
 Sterility 1943 Jan., 7  
     diagnosis, by general practitioner 1943 Jan., 55  
     endometrial biopsy in, 1943 Jan., 64  
     hormone therapy, 1943 Sept., 1383  
     1945 Jan., 258 261 Nov., 1403  
     Huhner test, 1943 Jan., 59  
     penicillin in, 1943 Jan., 113  
     psychiatric aspects 1945 Nov., 1521  
     Rubin test, 1943 Jan., 9 61  
     seminal examination 1943 Jan 60  
     Sternal puncture 1944 Jan., 157  
 Stiffness, simulated 1944 May 700  
 Stillbrestol 1943 Jan., 29 1944 Sept 1255  
     in amenorrhea, 1943 Jan., 38 Sept., 1375  
 Stillbrestol in dysmenorrhea, 1943 Sept., 1377 1945 Nov., 1413  
     in gonococcal vulvovaginitis, 1943 Jan., 76 1945 Nov., 1362  
     in menopause 1943 Jan., 40, Sept., 1382 1945 Nov., 1423  
     in polymenorrhea, 1944 Sept., 1227  
     in premenstrual tension, 1943 Sept., 1381  
     to stimulate ovulation, 1944 Sept., 1225, 1226  
 Still's disease, 1943 Sept., 1338  
 Stokes-Adams syndrome 1943 Nov., 1540  
 Stomach acidity in peptic ulcer 1944 March 408  
     carcinoma, diagnosis, 1945 March, 489  
     dyspepsia in, 1944 July 898  
     roentgen diagnosis, early 1944 Nov., 1352  
     contents, fractional analysis, 1944 Nov., 1516  
     distention, sensation of in functional disturbances, 1944 March, 419  
     hemorrhage from 1943 Nov., 1578  
     irritable, 1944 March 418  
     treatment 1943 Sept., 1385  
     psychosomatic disorders, 1944 Nov 1355  
     syphilis, dyspepsia in 1944 July, 900  
     ulcer See also *Peptic ulcer*  
         dyspepsia in 1944 July 895  
         vessels, sclerosis of 1944 May 728  
 Stools, character of in irritable colon, 1944 March 420  
 Strain, lumbosacral, acute, 1943 July 1066  
     postural backache due to, 1943 July, 1064  
     sacro iliac, acute, 1943 July, 1066  
 Stramonium in parkinsonism, 1944 March, 444  
 Strangulations, intestinal diagnosis, 1943 Nov., 1468  
 Streptococcal infections of eye, sulfonamides in 1944 July 793 794  
     sulfamerazine in, 1943 Nov., 1455  
     sulfonamides in 1943 Sept., 1253  
 Streptococcal meningitis, 1945 Sept., 1267  
     sulfonamides in 1944 July 870 872  
     sore throat, 1943 Sept. 1202  
     ulcerative colitis, sulfonamides in 1944 July 811  
 Streptococcus hemolyticus Infections, 1943 Sept., 1202  
     meningitis, 1943 Nov 1503  
     nonhemolytic, subacute bacterial endocarditis due to penicillin in 1945 Sept., 1129  
 Streptomycin in tuberculosis 1945 July 922  
 Streptotrichosis, 1945 March 340

- Stricture of urethra, acute retention due to, 1943 Nov, 1563
- Strophanthin in heart failure, 1945 March, 529
- Strumpell-Marie arthritis, 1943 Sept, 1338
- Strychnine poisoning, convulsions of, 1945 July, 889
- Stuttering, psychosomatic factors in, 1944 May, 615
- Subacromial bursitis, physical therapy in, 1943 July, 917
- Subarachnoid hemorrhage, 1943 Nov, 1554, 1557
- Subdeltoid bursitis, diathermy in, 1943 July, 1184
- physical therapy in, 1943 July, 917, 1012
- Subdural hematoma, 1943 Nov, 1557, 1945 Jan., 62
- chronic, diagnosis, importance of, 1945 July, 1042
- Succinylsulfathiazole See *Sulfasuxidine*
- Suction and pressure, intermittent, in occlusive arterial disease, 1943 July, 973, Sept, 1403
- Suicide tendencies in migraine and hypogonadism, 1943 Nov, 1630
- Suigenderism, 1944 May, 534, 535
- Sulfadiazine in adenoid bronchitis, 1944 Sept, 1095
- in bacillary dysentery, 1943 May, 695, Sept, 1208, 1218, 1944 Nov, 1507
- in bacteremia and meningitis, 1944 July, 872
- in bronchiolitis, acute, in infants, 1944 Sept, 1095
- in gonococcal infections, 1943 Jan, 76, Sept, 1254
- in women, 1944 July, 831
- in infectious arthritis, 1943 Sept, 1327
- in lymphogranuloma venereum, 1945 May, 682
- in meningitis, 1945 Sept, 1263
- in meningococcal infections, 1943 Sept, 1205
- Sulfapyrazine in pediatrics, 1944 July, 882, 884
- in otolaryngology, 1944 July, 797
- in pediatrics, 1944 July, 882, 884
- in pneumococcal meningitis, 1943 Nov, 1505
- in pneumonia, 1943 Sept, 1301, 1944 July, 808, Sept, 1068
- method and results in 533 cases, 1944 Jan, 267
- in puerperal sepsis, 1943 Nov, 1612, 1944 July, 829, 1945 Nov, 1487, 1489, 1490
- in pyelonephritis, 1943 Nov, 1562
- in rheumatic fever, prophylactic, 1945 March, 425
- Sulfapyrazine in staphylococcal infections, 1943 Sept, 1253
- in streptococcal infections, 1943 Sept, 1253, Nov, 1503
- in ulcerative colitis, streptococcal, 1944 July, 814
- in urinary tract infections, 1945 May, 576
- in women, 1944 July, 834
- toxic reactions, 1944 Jan, 275
- Sulfaguandine in bacillary dysentery, 1943 May, 695, Sept, 1219, 1254, Nov, 1482, 1944 July, 821, Nov, 1507
- in diverticulitis, 1944 July, 823
- in enteritis, regional, 1944 July, 821
- in ulcerative colitis due to venereal lymphogranuloma, 1944 July, 816
- regional, 1944 July, 819
- streptococcal, 1944 July, 814
- Sulfamerazine, clinical evaluation in 400 cases, 1943 Nov, 1447
- in bacteremia and meningitis, 1944 July, 872
- in meningococcal meningitis, 1943 Sept, 1205
- in otolaryngology, 1944 July, 798
- in pediatrics, 1944 July, 882, 884
- in pneumococcal pneumonia, 1945 March, 294
- in pneumonia, 1944 July, 809, 810, Sept, 1068
- in trachoma, 1944 July, 792
- toxic manifestations, 1943 Nov, 1457
- Sulfanilamide in bacillary dysentery, 1943 Sept, 1217
- in bacteremia and meningitis, 1944 July, 872
- in pediatrics, 1944 July, 884
- in plague, 1943 May, 761
- in pneumonia, 1944 July, 810
- in puerperal sepsis, 1944 July, 829
- in rheumatic infection, prophylactic, 1943 Sept, 1283, 1944 July, 838, 889
- in streptococcal infections, 1943 Sept, 1253, Nov, 1503
- in ulcerative colitis due to venereal lymphogranuloma, 1944 July, 815
- streptococcal, 1944 July, 813
- intrapertoneal, in gynecology, 1944 July, 833
- in pneumonia, 1944 Sept, 1069
- Sulfapyridine in bacillary dysentery, 1943 Sept, 1217
- in bacteremia and meningitis, 1944 July, 872
- in dermatitis herpetiformis, 1944 July, 846
- in gonorrhea, 1943 Jan, 76
- in gonorrheal conjunctivitis, 1944 July, 793
- vulvovaginitis, 1944 July, 834

- Sulfapyridine in plague, 1943 May, 761  
in pneumonia, 1944 July, 810  
in streptococcal infections, 1943 Nov., 1503  
in subacute bacterial endocarditis, 1944 Sept., 1133
- Sulfasuxidine in bacillary dysentery 1943 May, 695, Sept., 1208, 1225, 1254, 1944 July, 821 Nov., 1507, 1945 March, 426  
in carcinoma of intestine, 1944 July, 823  
in enteritis, regional 1944 July, 821  
in infectious diseases of colon, 1943 Jan., 189  
in ulcerative colitis, regional 1944 July 819
- Sulfathalidine in bacillary dysentery, 1945 March 426  
in chronic ulcerative colitis, 1945 March, 427  
in ulcerative colitis, regional, 1944 July, 819
- Sulfathiazole in bacillary dysentery 1943 May, 695, Sept. 1217, 1944 Nov., 1507  
in bacteremia and meningitis, 1944 July 872  
in enteritis, regional 1944 July, 821  
in gonorrhea 1944 March 506  
asymptomatic carrier states following 1944 March 508  
in women 1943 Jan 47 76, 93, 1944 July, 831  
in gonorrheal conjunctivitis, 1944 July, 793  
vulvovaginitis, 1944 July 834  
in infectious arthritis, 1943 Sept., 1327  
in influenza meningitis, 1943 Nov 1505  
in lymphogranuloma venereum 1945 May, 682  
in nasopharyngeal infections, by insufflation, 1944 Nov., 1331  
in pediatrics 1944 July 882 884  
in plague 1943 May 760  
in pneumonia, 1943 Sept. 1301 1944 July, 809 Sept. 1068  
in puerperal sepsis, 1943 Nov 1612 1944 July 829  
in pyelonephritis 1943 Nov., 1562  
in skin diseases, topical use 1944 July 847  
in staphylococcal infections, 1943 Sept 1253 Nov., 1506  
in ulcerative colitis due to venereal lymphogranuloma 1944 July 816  
streptococcal 1944 July 814  
in urinary tract infections, 1943 Sept., 1254 1945 May 576  
in women 1944 July 834  
intrauterine in gynecology, 1944 July 833
- Sulfonamides See also the individual drugs.  
alkali therapy with, 1944 July 878, Sept., 1070  
candy, 1944 July, 882  
comparative effectiveness against various organisms 1943 Sept. 1248  
crystals in urine, 1943 Nov., 1501  
dosage schedules, 1943 Sept., 1249, 1945 Sept., 1307  
effective blood concentrations, 1943 Sept. 1250  
gum 1944 July 882  
in arthropod borne virus encephalitis, 1943 May, 644  
in asthmatic patients, postoperative, 1944 July 995  
in bacillary dysentery 1943 May, 695 Sept., 1207 1208 1216 1254, Nov., 1482 1944 July, 821, Nov., 1507  
in bacteremia 1944 July, 869  
in brucellosis, 1943 Jan., 265, May, 716, 1945 March, 357  
in burns, 1943 Sept., 1231 1238  
in cavernous sinus thrombosis, 1945 July, 894  
in communicable diseases of children 1944 July 888  
in dermatology 1945 Sept., 1106  
indications and limitations, 1944 July, 844  
in diarrhea of infancy 1945 July, 884  
in diseases of infants and children 1944 July 887  
in dysentery 1945 Sept., 1311  
in children, 1944 July, 888  
in ear, nose and throat diseases 1944 July 797  
in elephantiasis, 1943 May, 869  
in gonococcal infections, 1943 Sept., 1254 1945 Sept. 1311  
in gonococcal vulvovaginitis, 1945 Nov., 1363  
in women 1943 Jan 47 76 93 1944 July 831  
in gynecology and obstetrics, 1944 July 827  
in hemolytic streptococcal infections, 1943 Sept. 1203  
in infectious arthritides 1943 Sept. 1327  
in infectious diseases of colon clinical evaluation 1943 Jan., 189  
in influenza 1944 Sept., 1077  
in intestinal diseases, 1944: July 811  
in lymphogranuloma venereum 1945 May 682  
in mastoiditis, 1944 July 799  
in meningitis 1943 Sept., 1204 1205 1253 Nov 1500 1505 1944 July 869 1945 Sept., 1263 1310  
in ophthalmology 1944 July, 789



- Sulfonamides in otitis media, 1944 July, 799  
 in otolaryngology in children, 1944 July, 887  
 local use, 1944 July, 801  
 in pediatrics, 1944 July, 882, 884  
 dosages, 1944 July, 884  
 modes of administration, 1944 July, 882  
 in plague, 1943 May, 760  
 in pneumonia, 1943 Sept., 1299, 1944 July, 805, 808, Sept., 1068, 1945 Sept., 1310  
 in children, 1944 July, 887  
 in primary atypical pneumonia, 1944 Sept., 1078  
 in puerperal sepsis, 1943 Nov., 1612, 1944 July, 828, 1945 Nov., 1487, 1489, 1537  
 in pyelonephritis, 1943 Nov., 1562  
 in rheumatic infection, prophylactic, 1943 Sept., 1283, 1944 July, 838, 889  
 in smallpox, 1943 May, 615  
 in staphylococcal infections, 1943 Sept., 1253, Nov., 1506  
 in streptococcal infections, 1943 Sept., 1253, Nov. 1503  
 in subacute bacterial endocarditis, 1944 Sept., 1132  
 in tuberculosis, 1945 March, 447  
 in ulcerative colitis, 1944 July, 811  
 in urinary tract infections, 1945 May, 574, 576, Sept., 1311  
 in children, 1944 July, 888  
 in women, 1944 July, 834  
 insoluble, in intestinal diseases, 1945 March, 426  
 intraperitoneal use, in gynecology, 1944 July, 833  
 lozenges, 1944 July, 882  
 niacin with, 1943 March, 578  
 parenteral use, in children, 1944 July, 883  
 pharmacology, 1944 July, 872  
 prophylactic uses, 1941 March, 473  
 rectal administration, in children, 1944 July, 882  
 renal complications, 1945 Sept., 1308  
 therapeutic failures, 1945 Sept., 1311  
 present status, 1943 Sept., 1247, 1945 Sept., 1306  
 toxic reactions, 1943 Sept., 1250, 1944 July, 876, 1945 Sept., 1308, 1309  
 urinary disturbances due to, in children, 1945 July, 877  
 lithiasis following, 1943 Nov., 1570  
 versus penicillin, 1945 May, 579  
 Sulkowitch test, 1943 Nov., 1629  
 in hyperparathyroidism, 1945 July, 1026  
 Supraorbital decompression in Graves' disease with severe exophthalmos, 1944 March, 493  
 Suprapatellar reflex in pyramidal tract lesions, 1945 Jan., 57  
 Suprapubic cystotomy, 1943 Nov., 1565  
 Suprarenal See *Adrenal*  
 Suprasellar cyst, obesity with, 1945 Sept., 1222  
 Suture, primary, in peripheral nerve injuries, 1945 Jan., 25  
 Swimming in relation to ears and sinuses, 1944 Sept., 1126  
 Synasol for snoring, 1944 Nov., 1331  
 in nasal allergy, 1944 Nov., 1335  
 Sympathectomy for essential hypertension, 1944 Sept., 1149  
 Sympathomimetic drugs, new, 1945 March, 419  
 Synapoidin, 1944 Sept., 1225  
 Syphilis, arsenotherapy, in pregnancy, 1945 Nov., 1466  
 cardiovascular, arsenotherapy, 1944 March, 305  
 electrocardiogram in, 1945 May, 606  
 dichlorophenarsene hydrochloride in, 1945 March, 438  
 early, arsenotherapy, intensive, 1944 March, 293  
 biweekly and triweekly systems, 1944 March, 298  
 combined with fever therapy, 1944 March, 297  
 five-day drip, 1944 March, 293  
 penicillin in, 1944 March, 302  
 eruptions of See *Syphilids*  
 esophagotracheobronchial fistula due to, 1944 July, 1004  
 in pregnant woman, management, 1945 Nov., 1463  
 latent, 1944 March, 302  
 intensive methods in, 1944 March, 303  
 of central nervous system, 1944 March, 303  
 of stomach, dyspepsia in, 1944 July, 900  
 of vulva, 1945 Nov., 1370  
 penicillin in, in pregnancy, 1945 Nov., 1468  
 toxemia of pregnancy and, 1945 Nov., 1437  
 treatment, recent advances, 1944 March, 293  
 Sumatra mite fever, 1944 Nov., 1464  
 Syphilitic aortitis, 1944 Jan., 70  
 aneurysm formation in, 1944 Jan., 71  
 arthritis, 1943 Sept., 1326  
 heart disease, 1943 Sept., 1288, 1944 Jan., 70  
 pregnancy and, 1945 Nov., 1450  
 optic atrophy, surgical treatment, 1944 March, 304, 446  
 Syringomyelia, treatment, 1944 March, 438

- Tarsus dorsalis*, treatment, 1944 March, 444  
*Tachycardia*, emotions and, 1944 May, 567  
*paroxysmal*, 1943 Nov., 1537 1945 Sept., 1154, 1156  
*digitalis* in, 1945 March, 531  
in children 1945 July, 873  
*magnesium sulfate* in 1945 March, 426  
*quinidine* in, 1945 Jan., 226  
*Talma* operation in cirrhosis of liver, 1945 March, 281  
*Tamponade*, cardiac, 1945 Sept. 1158  
*Tannic acid* in burns, 1943 Sept., 1232 1237  
*Tartar emetic* in African trypanosomiasis, 1943 May, 843  
*Taste*, hysterical affections, 1944 May 692  
*Teeth*, beneficial and harmful effects of fluorine on, 1944 Nov., 1428  
*nutrition* and, 1943 March, 545  
*Teething*, 1943 Nov 1525  
*Temperature*, basal graphs of timing of ovulation by, 1945 Nov., 1425  
*Tension headache*, 1944 March 439  
*Testes*, biopsy, 1944 Sept., 1246  
endocrine disorders of 1944 March, 482  
physiology, 1944 Sept., 1237  
*Testosterone* 1944 Sept., 1259  
clinical uses, 1944 Sept., 1257  
in angina pectoris prophylaxis, 1944 Jan., 29  
in amenorrhea, 1945 Nov., 1382  
in dysmenorrhea, 1943 Jan., 35, Sept., 1377 1945 Nov., 1413 1414  
in eunuchoidism 1944 March 482  
in frigidity 1943 Sept., 1383  
in functional uterine bleeding, 1943 Sept., 1379, 1945 Nov., 1385, 1399  
in gynecologic disorders, 1943 Jan., 33  
in hypermenorrhea 1944 Sept., 1223  
in menopause, 1943 Jan., 40 1945 Nov., 1407 1423  
in menorrhagia 1943 Jan., 38  
in menstrual disorders, 1945 Jan., 265  
in pituitary dwarfism, 1944 March, 476  
in premenstrual breast pain and secretions 1943 Sept., 1382  
in nephrosis, 1945 March, 436  
therapy advances in 1945 March 436  
*Testes*, functional of liver 1945 July 973  
pregnancy, 1945 Nov., 1553  
*Tetanus*, convulsions of, 1945 July 889  
*curare* in 1945 March 423  
immunization, 1945 Sept., 1244  
*Tetany* 1944 March 471  
in infants and children convulsions of, 1945 July, 890  
*parathyroid*, prevention 1945 March 402 434  
*Theelin*, 1944 Sept., 1254  
to stimulate ovulation, 1944 Sept., 1226  
*Theclol*, 1944 Sept., 1255  
*Theobromine* in angina pectoris prophylaxis, 1944 Jan., 27  
in coronary thrombosis, 1944 Jan., 7  
*Theophylline* and *mercural* orally in congestive heart failure, diuretic efficacy, 1944 July, 911  
in angina pectoris prophylaxis, 1944 Jan., 27  
*Thiamine* deficiency, 1943 March, 409  
central nervous system manifestations, 1943 March 431  
early, 1943 March, 495  
laboratory diagnosis, 1943 March, 504  
dosages, 1945 Sept., 1302  
enzyme relationships, 1943 March, 280  
in arthralgia of vitamin B deficiency, 1943 Sept. 1319  
in deficiency diseases, 1943 March, 274  
in facial pain 1945 Jan., 77  
in foods, 1943 March, 411  
in pregnancy, 1943 March, 540  
in radiation sickness, 1943 March, 577  
requirements, 1943 March, 292, 412  
*Thlouracil*, clinical development and application, 1945 March, 303 306  
in thyrotoxicosis, 1944 Sept., 1043 Nov., 1362 1945 March, 302 433  
toxicity, 1945 March, 307  
*Thomas pessary* 1943 Jan., 109 111  
*Thoracentesis*, 1945 March, 503  
in congestive heart failure 1944 March, 385  
*Thoracic disease*, nonsurgical emergencies, 1945 July, 837  
*Thoracoplasty* in tuberculosis 1945 March 449  
*Three-day fever* 1943 May, 808  
*Throat diseases* of chronic, 1944 March, 330  
new treatments, 1944 Nov., 1328  
*sulfonamides* in, 1944 July 797  
local use 1944 July 800  
sore, *sulfathiazole* by insufflation in 1944 Nov., 1331  
treatment, 1944 Sept., 1114  
*Thrombin*, uses of 1945 Sept., 1086  
*Thrombo-angitis obliterans* ischemic ulcers in *tyrothricin* for 1944 July 851 854  
physical medicine in 1943 July 951 1945 May 791  
*Thrombocytopenic purpura* 1944 Jan., 153  
essential 1944 Jan., 163  
symptomatic, 1944 Jan., 179  
*Thrombophlebitis*, puerperal 1945 Nov., 1492

- Thrombosis, 1943 Nov, 1545  
arterial, peripheral, 1943 Nov, 1546  
cerebral, 1943 Nov, 1554  
in children, 1945 July, 894  
coronary See *Coronary thrombosis*  
electrocardiogram in, 1945 May, 598  
pain of, differential diagnosis, 1945 March, 513  
quinidine in, 1945 Jan, 227  
restriction of activity in, and extent of myocardial infarction, 1945 March, 405  
mesenteric, 1943 Nov, 1552, 1944 May, 730  
of abdominal aorta, 1944 May, 733, 739  
of portal vein, 1944 May, 733  
prevention, dicoumarol in, 1945 July, 929  
heparin in, 1945 July, 933  
pulmonary, 1943 Nov, 1550  
venous, heparin in, 1945 March, 431  
peripheral, 1943 Nov, 1548  
Thrush, 1945 March, 323, 328  
Thymectomy for myasthenia gravis, 1945 Jan, 136  
Thymus, emergencies associated with, 1945 July, 860  
Thyroid deficiency, arthralgia due to, 1945 Sept, 1271  
desiccated, in hypothyroidism, 1944 March, 464  
extract, effects on electrocardiogram, 1945 May, 611  
in familial periodic paralysis, 1945 March, 422  
whole, 1944 Sept, 1269  
gland, diseases of, chronic, 1944 March, 467  
in soldiers overseas, 1944 Nov, 1527  
disturbances, real versus supposed, 1945 July, 1012  
hormone, 1944 Sept, 1238  
therapy in amenorrhea, 1945 Nov, 1382  
in Graves' disease with severe exophthalmos, 1944 March, 493  
in gynecologic disorders, 1943 Jan, 10, 34, 38  
in menopause, 1945 Nov, 1423  
Thyrotoxicosis, postoperative, 1944 March, 469  
thiouracil in, 1944 Sept, 1043, Nov, 1362, 1945 March, 302, 433  
Thyrotropic hormone, relation of exophthalmos to, 1944 March, 487  
Thyroxin, 1944 Sept, 1268, 1269  
in hypothyroidism, 1944 March, 469  
Tibia, lower end, ridging of, 1943 July, 1134  
Tibial nerve injuries, 1945 Jan, 22
- Tick fever See *Rocky Mountain spotted fever*  
African, 1943 May, 734  
vaccine, in prevention of Rocky Mountain spotted fever, 1944 May, 775  
Tinea, 1945 March, 323  
Tinnitus, 1944 Nov, 1327  
Tissue extracts in angina pectoris prophylaxis, 1944 Jan, 28  
Toad-skin, 1943 March, 356  
Tobacco, recurrent peptic ulcer and, 1945 Sept, 1169  
use of, in peptic ulcer, 1944 March, 412  
Toenails, ingrowing, 1943 July, 1143  
Tongue lesions See *Glossitis*  
Tonometry, 1944 May, 744  
Tonsillar hemorrhage, postoperative, treatment, 1944 Sept, 1118  
Tonsillectomy, diphtheria and, 1943 May, 655  
in adenoid bronchitis, 1944 Sept, 1095  
indications for, 1944 Nov, 1332  
Tonsillitis, acute, sulfonamides in, 1944 July, 799, 887  
bismuth in, 1944 Nov, 1332  
chronic, 1944 March, 332  
relation to systemic diseases, 1944 March, 333  
gonadal factors, 1944 Nov, 1331  
in infants, 1943 Nov, 1525  
Tonsils, pharyngeal, hypertrophy of, gonadal factors, 1944 Nov, 1330  
Topical applications, dermatologic, 1945 Sept, 1096  
Torticollis, spasmodic, treatment, 1944 March, 449  
Torula infection, 1944 July, 950  
Torulosis, 1945 March, 335  
Toxemia of burns, 1943 Sept, 1236  
of pregnancy, 1943 Nov, 1596, 1945 July, 848, Nov, 1435  
preeclamptic, 1945 July, 850  
prevention, 1943 Nov, 1597  
treatment, 1943 Nov, 1598  
Trachea, diseases of, chronic, pitfalls in diagnosis and treatment, 1944 March, 322  
tuberculosis of wall, without pulmonary involvement, 1944 March, 322  
tumor, probably syphilitic, laryngeal paralysis due to, 1944 March, 327  
Trachetis, atrophic, 1944 March, 326  
chronic membranous, 1944 March, 326  
with moss-agate sputum, 1944 March, 324  
Tracheo-esophageal fistula, 1944 July, 1001  
Trachoma, sulfamerazine in, 1944 July, 792  
Tractotomy, medullary, for facial pain, 1945 Jan, 84

- Transference to psychotherapy, 1944 May 550  
 Transfusions blood in aemia 1944 March, 380  
     in bronchiolitis, acute, in infants, 1944 Sept., 1104  
     in erythroblastosis foetalis 1944 Jan., 251 263  
     in gastrointestinal hemorrhage 1943 Nov., 1579  
     in hemolytic anemia, 1945 May, 703  
     in hemorrhage 1943 Nov 1544  
         of pregnancy and labor 1943 Nov 1611  
     in leukemia 1944 Nov 1384 1385  
     in pernicious aemia, 1945 Jan 245  
     in pregnancy, 1944 Jan., 250 264  
     in puerperal sepsis 1943 Nov., 1612  
     in subacute leukemia, 1944 Jan 190  
     in thrombocytopenic purpura 1944 Jan., 158  
     in uodulant fever, 1943 Jan. 267  
     indications 1943 Jan., 164 1945 Sept., 1075  
     new developments 1945 Sept., 1076  
     reactions, 1945 Sept., 1088  
     prevention 1944 Jan 250 263  
     repeated, testing for Rh factor in 1944 Jan., 250  
     Rh factor in 1944 Jan 236 250  
         256 March 379 1945 Sept., 1076  
     of immune blood, 1943 Jan., 157  
     plasma 1943 March 310  
 Transverse processes, fractures, 1943 July 1079  
 Traumatic neuroses 1944 May 663  
 Treatment specific methods symposium on, 1943 Sept., 1201 1944 Sept., 1029  
 Tremor neurasthenic, 1944 May 676  
     simulated 1944 May 702  
 Trench foot 1943 July 1148  
     hypothermia in, 1943 July 1173  
 Trends, modern in internal medicine 1945 May 563  
 Trichinosis, electrocardiogram in 1945 May 607  
 Trichlorethylene in facial pain 1945 Jan., 77  
 Trichomonas vaginitis 1943 Jan., 4 45  
     1945 Nov., 1357  
 Trichophylin test for dermatophytosis 1945 March 325  
 Trichophytosis, 1945 March 323  
 Tridione in epilepsy 1945 Sept., 1122, 1124  
 Trigeminal neuralgia 1945 Jan., 73  
     atypical, 1945 Jan., 85  
     symptomatic 1945 Jan 75  
 Trigger zones in trigeminal neuralgia, 1945 Jan., 74  
 Trigonitis, chronic granular 1945 Sept., 1207  
 Trihydroxyestrin, 1944 Sept., 1255  
 Trömmner's technic for Hoffmann sign, 1945 Jan., 54  
 Tropical diseases of concern to the home front 1943 Nov., 1476  
     postwar aspects 1945 July, 897  
     symposium on 1943 May, 601  
 Trypanosoma congolense, 1943 May, 843  
     cruzi 1943 May 824  
     gambiense, 1943 May, 835  
     rhodesiense, 1943 May, 836  
 Trypanosomiasis African 1943 May, 835, Nov., 1491  
     American 1943 May, 822 Nov., 1492  
     Brazilian, 1943 May, 822  
     postwar problem of, 1945 July, 906  
 Tryparamide in African trypanosomiasis 1943 May, 845  
 Tsutsugamushi disease, 1944 Nov., 1464  
 Tuamlae sulfate, 1945 March, 420  
 Tubal patency, Rubin test, 1943 Jan., 9 61  
 Tuberculosis, chemotherapy 1945 March 445 July, 918  
     diascopic in 1945 March 447, 448, July 921  
     esophagotracheobronchial fistula due to 1944 July 1004  
     of bones and joints, physical therapy to 1943 July 915  
     of kidney, 1944 Sept., 1185  
     of tracheal wall without pulmonary involvement, 1944 March 322  
     of vulva, 1945 Nov., 1369  
     physical medicine in 1945 May 792  
     pregnancy and, 1945 Nov., 1454  
     promin in, 1945 March 447 448 July, 919  
     promizole in 1945 July 921  
     pulmonary asymptomatic case, management, 1945 March 550  
     diabetes mellitus and, association of, 1944 March 493  
     hemoptysis in 1945 July, 837  
     modern methods of finding 1945 March 544  
     penicillin failure in 1945 May 587  
     pleural effusions of, 1945 March, 507 511  
     surgical treatment 1945 March 449  
     treatment, recent advances 1945 March, 445  
     streptomycin in 1945 July 922  
 Tuberculous arthritis, 1943 Sept., 1326  
 Infections sulfamerazine in 1943 Nov., 1456  
     meningitis 1945 Sept., 1267  
 Tularemia pleural effusion in, 1945 March, 508  
 Tumors, facial pain due to 1945 Jan., 91  
     of brain in children 1945 July, 892

- Tumors of rectum, rectosigmoid and colon, errors in diagnosis, 1944 Jan, 278
- Tympanic membrane, perforations, 1944 March, 334
- Typhoid fever, immunization, 1945 Sept, 1245  
vaccine therapy in rheumatoid arthritis, 1943 July, 1125
- Typhoid-dysentery infections in infants and children, 1944 Sept, 1190
- Typhus exanthematicus, 1943 May, 775  
fever, 1943 May, 775  
endemic or murine, 1943 May, 775, 784, 787  
epidemic, 1943 May, 775, 779, 782  
louse-borne, postwar problem of, 1945 July, 900  
scrub or mite, 1944 Nov, 1464
- Tyrosine in ulcers of extremities due to peripheral vascular disease, 1944 July, 849
- ULCER, duodenal See *Duodenal ulcer* and *Peptic ulcer*  
gastric See *Stomach ulcer* and *Peptic ulcer*  
Hunner's, 1945 Sept, 1205  
ischemic, tyrosine in, 1944 July, 851, 854, 855  
of extremities due to peripheral vascular disease, tyrosine in, 1944 July, 849  
peptic See *Peptic ulcer*  
skin, sulfathiazole in, topically, 1944 July, 847  
venous stasis, tyrosine in, 1944 July, 850, 853
- Ulnar nerve injuries, 1945 Jan, 15
- Ulnar-median nerve injuries, 1945 Jan., 18
- Ultraviolet irradiation, continuous disinfection of air by, 1944 Nov, 1306  
in rickets, 1943 March, 366
- Undecylenate-undecylenic acid ointment in dermatophytosis, 1945 March, 326
- Undulant fever See *Brucellosis*
- Unna's boot, 1943 July, 958
- Urea as diuretic, 1944 Sept, 1181  
in congestive heart failure, 1944 March, 385  
blood, in liver disease, 1945 July, 980
- Uremia, convulsions of, 1945 July, 891
- Urethra, caruncle, 1945 July, 1007  
diverticulum, 1945 July, 1008  
female, certain conditions of, 1945 July, 1005  
foreign body in, acute retention due to, 1943 Nov, 1566  
mucosa, prolapse of, 1945 July, 1007  
stricture, acute retention due to, 1943 Nov, 1563
- Urethral catheters, 1943 Nov, 1563, 1564  
smears, 1943 Jan, 90
- Urethritis, chronic granular, 1945 Sept, 1207  
gonorrheal, anterior, 1944 March, 512  
posterior, 1944 March, 513  
in female, 1945 July, 1006
- Urgin in heart failure, 1945 March, 529
- Urinalysis in office gynecology, 1943 Jan, 1
- Urinary lithiasis following sulfonamides, 1943 Nov, 1570  
tract infections, chemotherapy, 1943 Sept, 1254, 1944 July, 825, 834, 888, 1945 May, 574, 575, Sept, 1311  
chronic, 1943 Jan, 236  
nontuberculous, treatment, 1945 May, 571  
sulfonamides in, 1943 Sept, 1254, 1944 July, 825  
in children, 1944 July, 888  
in women, 1944 July, 834  
nonsurgical emergencies, in children, 1945 July, 874
- Urine concentration tests in Addison's disease, 1944 Sept, 1244  
in diabetes insipidus, 1944 Sept, 1244  
in hypertension, 1943 Sept, 1267  
constituents, 1945 Sept, 1321  
laboratory findings, in health and disease, 1945 Sept, 1314  
retention, acute, 1943 Nov, 1562  
hysterical, hypnosis in, 1944 May, 648  
tests in endocrinology, 1944 Sept, 1242
- Urobilinogen test of liver function, 1945 July, 978
- Urologic symptoms in gynecologic disorders, 1943 Jan, 13
- Uterine bleeding, functional, hormone therapy, 1943 Sept, 1378, 1945 Jan, 259, 261, 264, 266, Nov, 1398  
treatment, 1945 Nov, 1384
- Uterus, carcinoma, diagnosis, vaginal smear for, 1945 Nov, 1551  
cervix See *Cervix uteri*  
nonreplaceable, pessaries in, 1943 Jan, 114  
prolapse, pessaries in, 1943 Jan, 11, 115  
retrodisplacements, pessaries in, 1943 Jan, 11, 109
- VACCINATION during pregnancy as prophylaxis against puerperal infection, 1945 Nov, 1495
- Vaccines in arthropod-borne virus encephalitis, prophylaxis, 1943 May, 645  
in bacillary dysentery, 1943 Sept, 1216  
in brucellosis, 1943 Jan, 265, May, 715, 1945 March, 358  
in cholera prophylaxis, 1943 May, 774

- Vaccines in elephantiasis 1943 May, 868  
in endemic typhus fever prophylaxis 1943 May, 788  
in epidemic typhus fever prophylaxis 1943 May, 783  
in lymphogranuloma venereum, 1945 May, 683  
in plague prophylaxis, 1943 May, 763  
in Rocky Mountain spotted fever prophylaxis 1943 May, 732, 1944 May, 776  
in von Economo's encephalitis, 1943 May 648  
Vagina diseases, as cause of leukorrhea, 1943 Jan., 45  
normal, biology of, 1943 Nov., 1354  
Vaginal bleeding 1943 Jan., 6  
excessive, in young girl 1943 Jan., 20  
smears, 1944 Sept., 1245  
for ovarian function and uterine cancer, 1945 Nov., 1548  
Vaginismus, 1945 Nov., 1372  
Vaginitis, 1945 Nov., 1356  
atrophic, 1945 Nov., 1356  
bacterial, various types 1943 Jan., 46  
due to hyperestrogenism 1943 Jan., 48  
fusospirochetal, 1945 Nov., 1361  
gonorrheal, 1943 Jan. 5 46  
in infants, 1943 Nov., 1527  
sulfonamides in 1944 July 834  
monilia, 1943 Jan., 5 46, 1945 Nov., 1360  
nonspecific, 1943 Jan., 5, 46, 1945 Nov., 1355  
puerperal 1945 Nov., 1485  
senile 1943 Jan 40 49  
treatment, advances in 1945 Nov., 1354  
trichomonas, 1943 Jan., 4 45 1945 Nov., 1357  
Valvular disease, rheumatic, chronic, 1945 Sept., 1282  
Van den Bergh test, 1945 July 975  
Vaponefrin in bronchial asthma, 1944 March 346 350  
Vapors, germicidal disinfection of air with, 1944 Nov., 1309  
Variola See Smallpox  
Vascular conditions, emotions in, 1944 May 572  
diseases, peripheral, ulcers of extremities due to tyrothridin in 1944 July 849  
physical medicine in 1943 July, 951  
emergencies, 1943 Nov., 1542  
extracardiac, 1943 Nov., 1540  
occlusion, 1943 Nov., 1545  
mesenteric, 1943 Nov., 1552  
miscellaneous, 1943 Nov., 1552  
physiology, recent advances, therapeutic implications, 1943 Sept., 1397  
Vasospasm 1943 Nov., 1546  
Venous compression, intermittent, in peripheral vascular disease, 1943 July, 981, Sept., 1402  
insufficiency, prevention of edema, 1943 July, 958  
stasis ulcer, tyrothridin in, 1944 July, 850, 853  
thrombosis, deep, peripheral, 1943 Nov., 1348  
Ventricular failure, left, acute, 1943 Nov., 1535  
versus right, 1943 Jan., 121, 135  
gradient, 1945 March 464  
tachycardia, paroxysmal 1943 Sept., 1156  
Veritol, 1945 March, 420  
venilis, 1944 July, 969  
Vertebral bodies, fractures, 1943 July, 1080  
Vesania, 1945 Jan., 147  
Vibration test for sensory disturbance, 1944 July, 938  
Vibrio comma 1943 May, 766  
Vincent's infection, nutrition and, 1943 March, 550  
of vagina, 1945 Nov., 1361  
of vulva, 1945 Nov., 1370  
vitamin therapy, 1944 Nov., 1332  
Vioform in amebiasis, 1943 May, 691  
Vioosterol in rickets, 1943 March 368  
sulfamerazine in, 1943 Nov., 1456  
Virus pneumonia 1943 Sept., 1293  
Vision, hysteric affections, 1944 May, 691  
neurasthenic affections, 1944 May 676  
Visual disturbances, simulated 1944 July, 938  
Vitamin A, 1943 March 349  
deficiency 1943 March 349 355  
diet in, 1945 May, 803  
early, 1943 March 495  
laboratory diagnosis, 1943 March, 503  
pathology, 1943 March 512  
wound healing and 1943 March, 564  
dosages, 1945 Sept., 1301  
in pregnancy 1943 March, 539  
requirements, 1943 March, 291 352  
Vitamin B See also Thiamine, Nicotinic acid and Riboflavin  
deficiency arthralgia in 1943 Sept., 1317  
diet in, 1945 May, 803  
electrocardiograms in, 1945 May 603  
dosages, 1945 Sept., 1302  
Vitamin C. See also Ascorbic acid  
in bronchial asthma 1945 March 460  
Vitamin D, 1943 March 362  
deficiency See Rickets  
in pregnancy 1943 March 541

- Vitamin D in rheumatoid arthritis, 1944 March, 314  
 in rickets, 1943 March, 366  
 massive doses, in prevention of parathyroid tetany, 1945 March, 434
- Vitamin D<sub>2</sub>, 1944 Sept., 1265
- Vitamin K, 1943 March, 371  
 deficiency, 1943 March, 371  
 early, 1943 March, 495  
 pathology, 1943 March, 517  
 in acute cholecystitis, 1943 Nov., 1586  
 in hemorrhagic disease of newborn, 1943 March, 377  
 laboratory tests, 1943 March, 372  
 massive doses, with dicoumarol, 1945 March, 430  
 preparations, dosages, and administration, 1943 March, 375  
 preoperative use, 1943 March, 377  
 relation to prothrombin, 1943 March, 372
- Vitamin therapy, general rules, 1943 March, 579  
 in cirrhosis of liver, 1945 March, 279  
 in deafness, 1944 Nov., 1325  
 in deficiency diseases, 1943 March, 274, 533  
 early cases, 1943 March, 496  
 in eye lesions, 1943 March, 558  
 in gastrointestinal hemorrhage, 1943 Nov., 1583  
 in irritable stomach, 1943 Sept., 1392  
 in pernicious anemia, 1945 Jan., 244  
 in various conditions, 1943 March, 577  
 in Vincent's infection, 1944 Nov., 1332
- Vitamin "U" in special convalescent ulcer diet, 1945 May, 709
- Vitamins, concentrates, 1943 March, 533  
 deficiencies, causes, 1945 Sept., 1295  
 diagnosis, 1945 Sept., 1296  
 early, 1943 March, 485  
 evidences of, 1943 Sept., 1365  
 laboratory tests, 1943 March, 501  
 mixed nature of, 1943 March, 274  
 pathology, 1943 March, 509  
 rôle of gastrointestinal tract in conditioning, 1943 March, 519  
 treatment, 1945 Sept., 1301  
 enzyme relationships, 1943 March, 280  
 in dermatology, 1945 Sept., 1109  
 in infant feeding, 1943 Sept., 1359, 1363  
 in pregnancy, 1943 March, 539  
 in present day treatment, 1945 Sept., 1294  
 in various conditions, 1943 March, 577  
 massive doses, 1943 March, 534  
 in deficiency diseases, 1943 March, 274, 572  
 synthetic, 1943 March, 533
- Voice test of hearing, 1944 Nov., 1325
- Vollmann's ischemic myositis, physical therapy in, 1943 July, 917
- Vomiting, deficiency state due to, 1943 March, 523  
 of pregnancy, 1945 Nov., 1436, 1444  
 pernicious, of pregnancy, 1945 July, 848
- Von Economo's type of encephalitis, 1943 May, 646, Nov., 1507
- Vulva, diseases of, 1945 Nov., 1365
- Vulvitis, puerperal, 1945 Nov., 1485
- Vulvovaginitis, gonococcal, 1943 Jan., 67, 1945 Nov., 1362  
 sulfonamides in, 1944 July, 834
- WAR neuroses, 1945 May, 729  
 theaters, psychiatric disturbances in, 1945 May, 729
- Warm dressings, sterile, in peripheral vascular disease, 1943 July, 951
- Warts, plantar, 1943 July, 1143  
 semile, 1944 July, 969
- Wasserhelle cell, 1945 March, 400
- Water requirement in kidney disease, 1944 Sept., 1176
- Waterhouse-Friderichsen disease, 1943 Nov., 1624
- Weight, normal, for boys, girls, men and women, 1943 March, 327
- Weil-Felix reaction in Rocky Mountain spotted fever, 1943 May, 730  
 in typhus fever, 1943 May, 781
- Werlhof's disease, 1944 Jan., 163
- Wernicke's disease, 1943 March, 415, 514
- West Nile fever, 1943 Nov., 1516
- Western equine type of encephalitis, 1943 May, 633
- Wet dressings, continuous, in peripheral vascular disease, 1943 July, 951  
 in acute dermatitis, 1945 July, 834  
 in skin disease, 1945 Sept., 1096
- White blood count, peripheral, interpretation of, 1944 July, 920
- Whooping cough, 1943 Nov., 1529  
 immunization, 1945 Sept., 1242
- Winterbottom's sign, 1943 May, 839
- Wound healing, nutrition and, 1943 March, 561
- Wounds, self-inflicted, suspected, 1944 July, 939  
 sulfonamides in, topically, 1944 July, 847
- Wright-Giemsa stain for malarial parasite, 1944 Nov., 1459
- Wrist clonus in pyramidal tract lesions, 1945 Jan., 57
- Wuchereria bancrofti, 1943 May, 862
- XANTHINE diuretics in congestive heart failure, 1944 March, 385

- |  |  |
|--|--|
| <p> Venodiagnosis in American trypanosomi-<br/> asis, 1943 May, 829<br/> Xerophthalmia, 1943 March, 357<br/> x Ray See Roentgen<br/>     treatment of conductive deafness due<br/>     to lymphoid hyperplasia of naso-<br/>     pharynx 1945 Sept., 1251 </p> | <p> Yaws 1943 Nov., 1495<br/> Yeast brewers', dosages 1945 Sept., 1303<br/> Yellow fever, 1943 Nov., 1487<br/>     postwar problem of, 1945 July, 898<br/> <br/> Zinc, as nutrient, 1943 March, 284 </p> |
|--|--|





